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The promptness with which Casec checks diarrheal stools is an important factor in arresting the dehydration which makes infantile diarrhea so serious a clinical problem. At the same time Casec replenishes calcium lost through the stools. Casec's high protein content, moreover, serves to promote growth of new tissue in infants who have become wasted as the result of diarrhea.

Casec is especially indicated for loose stools in breast-fed infants, fermentative diarrhea in bottle-fed babies, and diarrhea in older children.

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The Journal of Pediatrics

VOL. 6 FEBRUARY, 1935 NO. 2

Original Communications

THE INTRAVENOUS ADMINISTRATION OF FAT

A PRACTICAL THERAPEUTIC PROCEDURE

L. EMMETT HOLT, JR., M.D., HERBERT C. TIDWELL, PH.D., AND T. F. MCNAIR SCOTT, M.D.

BALTIMORE, MD.

ALTHOUGH fat emulsions have been injected intravenously into animals by a number of different investigators, two obstacles have prevented the successful application of this procedure to man—the difficulty of obtaining an emulsion stable enough to resist sterilization and the danger of fat embolism. A few brave souls, to be sure, have given small amounts of fat by this route. Bondi and Neumann[1] made ultramicroscopic observations on the disappearance of injected fat particles from the blood stream, and Saxl and Donath[2] used this procedure as a clinical test for the activity of the reticuloendothelial system, it being supposed that fat particles injected into the circulating blood were removed by the phagocytic cells. During the Great War emulsified,[3] and even unemulsified, camphorated oil[4] was given intravenously, no dire consequences being recorded. It is only in recent years, however, that a technic has been developed whereby large quantities of emulsified fat could safely be administered. Credit for this achievement belongs to Yamakawa and his associates, who carried out a series of experimental and clinical studies[5] in this field. They found that by using egg lecithin in sufficient quantities as an emulsifying agent it was possible to make emulsions that would resist sterilization by heat. By homogenization they produced emulsions in which practically none of the particles exceeded 2 μ in diameter, fine enough to pass without difficulty through

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The expenses of this investigation were defrayed in part by a grant from Mead Johnson and Company, Evansville, Ind.

the lung capillaries.* The practical difficulties which had stood in the way of intravenous fat therapy thus appeared to have been solved.

It is clear that intravenous fat administration, if feasible, will have important therapeutic applications. As a parenteral food it should be of value in medical or surgical conditions demanding rest for the gastrointestinal tract; it offers particular advantages in infants with nutritional disorders who cannot digest adequate quantities of food given by mouth and whose fat reserves are readily depleted. As a means of introducing calories, fat is more efficient than carbohydrate, and it may well be that it serves other more specific purposes as well. Adequate proof of this last possibility has not been presented, but the observations of the Burrs[7] on essential fatty acids, of Helmholz[8] on the bactericidal action of ketogenic diets, of Hanger[9] and others on the effect of lipids in immune reactions, of Hansen[10] on the influence of particular lipids in eczema, and of Harrop[11] on the importance of certain lipids in adrenal insufficiency are certainly suggestive.

Various histologic and chemical studies have been made to ascertain the fate of fat introduced by vein. As stated above, when the particles are too large, much of the fat is caught in the lungs, but when the emulsion is sufficiently fine, the bulk of the fat is removed from the circulation by the liver,[12] smaller portions being recoverable from the other organs and fat depots; at the height of lipemia fat may even appear in the urine. Although some observers[2,13] have found that fat particles accumulated in the phagocytic cells belonging to the reticuloendothelial system, there is equally definite evidence[14] against this; even after moderately large doses of fat the organs have been found to present no histologic peculiarities, fat particles being present only in the parenchymal cells. We ourselves, in collaboration with Dr. G. Lyman Duff, of the Department of Pathology, have made observations on six dogs given fat by vein, and we can confirm the finding that fat globules are visible only in the parenchymal cells unless the dose of fat has been extreme. Possibly the discrepancies in the literature are due to the use of different preparations.

The evidence in regard to the combustion of fat introduced by vein is not as complete as could be desired. Observations in man are wanting.† Murlin and Riche[15] followed the respiratory quotient in two dogs after intravenous fat administration, finding changes comparable to those observed by Murlin and Lusk[16] in dogs receiving fat by mouth. On the other hand, Nomura[17] working with rabbits was able to demonstrate the combustion of fat given by vein only when the animal's fat reserves had

*It is a curious fact that fat particles 4μ in diameter tend to be caught in the lung capillaries[6] although red blood cells of twice this diameter pass through without difficulty.

†Since this was written we have had the opportunity of seeing a paper by H. Gordon and S. Z. Levine (Am. J. Dis. Child. in press) presenting calorimetric data on infants, which suggests that fat introduced by vein is promptly burned.

been depleted by starvation. Baba[27] was able to demonstrate a fall in the respiratory quotient after the intravenous administration of fat in depancreatized rabbits or those treated with thyroxin.

Two clinical studies of parenteral feeding with intravenous fat have been published. Yamakawa's emulsion was developed for patients with peptic ulcer, and he and Nomura[18] reported that several hundred patients had been so treated with satisfactory results, as much as 300 c.c. being administered at one time. Valledor, Casas, and Gomez del Rio[19] reported a small series of infants with marasmus, in whom intravenous fat injections caused most encouraging results.

PERSONAL OBSERVATIONS

When our own studies were commenced, we were unfamiliar with the work of the Japanese investigators, but after trying various emulsifying agents* including soaps, bile salts, and cholesterol, we reached the same conclusion as had Yamakawa—namely, that lecithin was the most satisfactory agent available. Moreover, it seemed logical to use lecithin because of the work of Best and Hershey,[20] which appeared at about that time, showing that lecithin and closely related substances would prevent the accumulation of fat in the liver of the depancreatized animal. We have prepared lecithin emulsions similar to that of Yamakawa, except in regard to the type of fat, which was varied, and we have also made some observations with the Yamakawa emulsion itself.†

The Japanese emulsion contains 6.9 per cent total lipids suspended in distilled water; a trifle less than half of the lipid material is said to be egg lecithin, the remainder being a mixture of butter and cod liver oil. Our own emulsions contained from 7 to 7.5 per cent lipids. About one-third of this material consisted of fresh commercial egg lecithin, rectified with petroleum ether; the remainder consisted of various fats: olive oil, cocoanut oil, soy bean oil, butter, or human body fat. We have avoided cod liver oil on theoretical grounds since there is evidence[21] that it contains certain long chain, highly unsaturated fatty acids that are not readily burned and tend to accumulate in the liver. Our emulsions were homogenized at 4,000 pounds' pressure and were then sterilized by autoclaving. Most of the fat particles were less than 2 μ in diameter, only a few being as large as 3 μ. The emulsions were rendered isotonic just before use by diluting with one-tenth their volume of ten times physiologic saline.

After convincing ourselves that the injection of such preparations was attended by no risk, we proceeded to make a comparison of the various

*Much of this work was done by Dr. Warren M. Cox, Jr., who was associated with us at that time.

†Marketed by the pharmaceutical house of Sankyo in Tokio under the name "Yanol."

fats mentioned as regards the rate of disappearance from the blood stream after intravenous injection. The injections were given to normal infants following a twelve-hour fast; observations on the blood fat* were made just before the injection and at regular intervals thereafter. The quantity injected was arbitrarily chosen as 1 gm. of total lipid per kilogram of body weight.

Our findings were altogether negative as far as the comparison of different fats was concerned. The type of lipemic curve varied to some extent in different individuals but was independent of the type of fat given. Typical curves are shown in Charts 1 and 2. This result might be interpreted as showing that the fats studied were equally well assimilated; a more probable explanation is that the rate of removal from

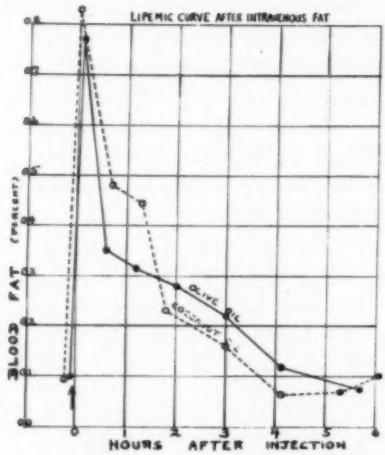

Chart 1.—Baby C—s. Quantity: 1 gm. fat per kilogram. Fasted before test.

the blood stream is determined by the lecithin coating of the particle. We studied one dog after an injection of mineral oil emulsified with lecithin and obtained a curve not appreciably different from that observed with emulsions of edible fats.

Although we had not succeeded in demonstrating that one fat was more readily assimilated than another when introduced intravenously, our therapeutic observations have been made almost exclusively with lecithin emulsions of olive oil. This seemed to give more stable emulsions than most of the fats we tried; moreover, our balance studies[23] had shown that this fat was exceptionally well absorbed from the intestine, and it

*The determinations of blood fat were made by Mr. R. J. Myers and Miss E. G. Nichols, using a modification of the micromethod of Gorter and Grendel[22]. The extraction was made with ethyl ether from whole blood samples, air dried on fat-free filter paper. This procedure extracts all neutral fat and free cholesterol, traces of cholesterol esters, but no phospholipids.

seemed possible that other tissues might handle it more readily. Mills[24] found it particularly bland when introduced subcutaneously.

THERAPEUTIC RESULTS

Up to the present time we have used these emulsions for purposes of parenteral feeding in sixteen infants with severe nutritional disorders, who received from 2 to 7 injections apiece on successive days; the dose was 1 gm. of lipid per kilogram in all but a few instances in which twice that quantity was given. Our experience has thus not been very extensive, and the present report must be regarded as a preliminary one. From our data it is not possible to form an unequivocal judgment as to the value of the treatment. A number of these cases were hopeless from the start—they were infants with tuberculous or pyogenic menin-

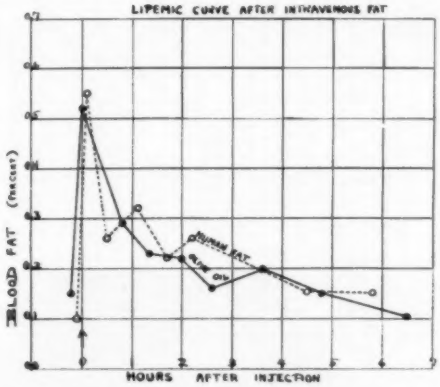

Chart 2.—Baby C—y. Quantity: 1 gm. fat per kilogram. Fasted before test.

gitis, peritonitis, or septicemia; the fatal outcome which ensued can hardly be held against the treatment. In other instances even though recovery took place, it cannot be credited to the treatment, for other therapeutic measures—fluids, transfusions—were simultaneously given. We shall present a few case histories, however, in which we gained the impression that the treatment had been responsible for improvement.

Case 1.—(H. L. H., No. 83915.) This was a full-term baby, birth weight unknown, who weighed 6½ pounds (2,955 gm.) when two weeks old. He was grossly underfed and lost weight steadily. The bowels alternated between constipation and "starvation diarrhea." At no time was there any evidence of infection.

The patient was admitted to the hospital at the age of three and one-half months weighing 4 pounds, 12 ounces (2,170 gm.); he was extremely emaciated and somewhat dehydrated. The dehydration was controlled by a single injection of intraperitoneal saline. A diet was given providing 125 calories per kilogram, which was gradually increased to 200 calories during the first week. Two transfusions were given during this period and were followed by mild reactions. Except for the

initial gain following the saline infusion, the patient's weight remained stationary during the first week and the first five days of the second week in the hospital, even though he was receiving 200 calories per kilogram during this latter period.

Three fat injections were then given on successive days. After the second one the weight began to rise abruptly. A week later a second series of three injections on alternate days caused an accelerated gain of weight at that time. The patient continued to thrive, weighing 13 pounds, 4 ounces (6,135 gm.) at the age of six and a half months.

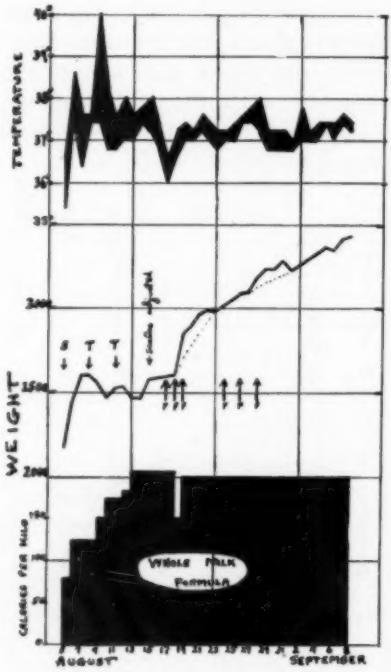

Chart 3.—Case 1 (A. S.).

Although it seems likely that this patient would have started to gain sooner or later regardless of the fat injections, it is nevertheless striking that the gain in weight was so marked and coincided so closely with the administration of fat.

The following two cases were infants suffering from extreme malnutrition caused by diarrhea associated with infection of the upper respiratory tract:

Case 2.—(H. L. H., No. 85259; Unit No. 49135.) A twin, born on the obstetric service of the Johns Hopkins Hospital, progressed satisfactorily for one month but then began to refuse food, lost weight, and developed diarrhea. Pharyngitis and otitis media were noted subsequently. Subcutaneous saline was administered several times to overcome dehydration. The patient continued to lose weight and became

extremely emaciated, the features being pinched and the fat pads of the cheeks practically absent. Under the influence of daily fat injections and transfusions, marked improvement took place, leading to eventual recovery.

It is worthy of comment here that saline alone (given prior to September 26) failed to check the loss of weight. With the introduction of intravenous fat (September 26 to 28) the weight increased, and there was improvement in the general appearance, despite a small peak in the temperature curve. The subsequent improvement (September 28

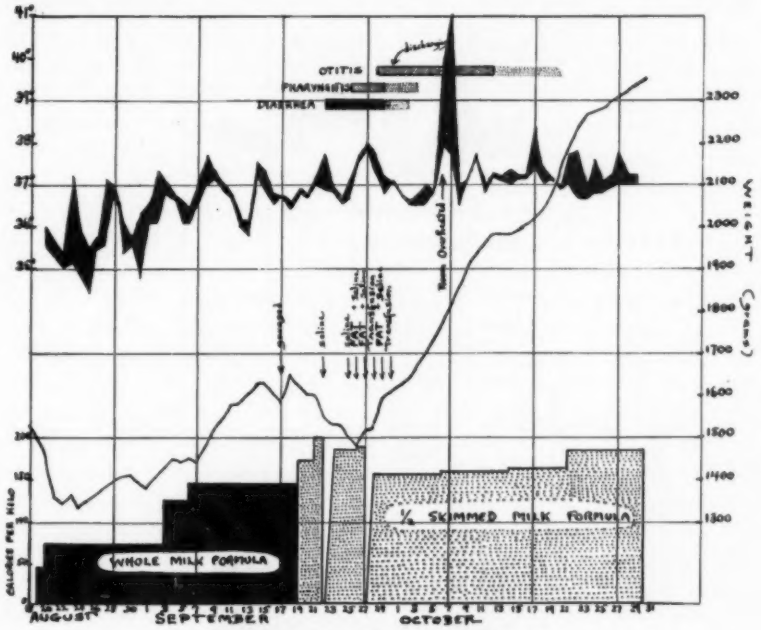

Chart 4.—Case 2 (M. L. H., Twin B).

onward) cannot be credited to the fat, for transfusions, drainage of the middle ear, fall in temperature, and amelioration of the diarrhea doubtless contributed to this.

CASE 3.—(H. L. H., No. 84781.) A full-term infant, weighing 8¼ pounds at birth (3,750 gm.), was admitted to the hospital at the age of two months, having lost 2 pounds in weight. There was a history of a nasal discharge, almost continuous since birth, and refusal of food; he had been given standard feedings. The patient was extremely malnourished, and in addition to rhinitis, there were râles in the chest and a low-grade fever.

For three weeks the patient improved; the bronchitis cleared up though some nasal discharge persisted; after a single set-back he seemed to be gaining weight. But on December 23 he developed a diarrhea with an exacerbation of the nasal discharge. Two days later there was evidence of dehydration, and parenteral saline was ad-

ministered; the feedings were omitted for part of a day and then gradually increased. On December 27 the patient's condition was critical. The nasal discharge was extremely profuse, suggesting sinusitis; the diarrhea, which had abated with the reduction in food, reappeared promptly when this was increased to 70 calories per kilogram. It was clear that a further period of therapeutic starvation would not be tolerated, for malnutrition was extreme; the fat pads of the cheeks had gone entirely. It was decided to offer the patient 40 calories per kilogram by mouth and to supply 15 calories per kilogram each day in the form of intravenous fat. Within forty-eight hours there was a marked change for the better in the child's appearance; the fat pads became palpable in the cheeks; the stools likewise were improved. The fat injections were kept up for six days, until the oral feeding had

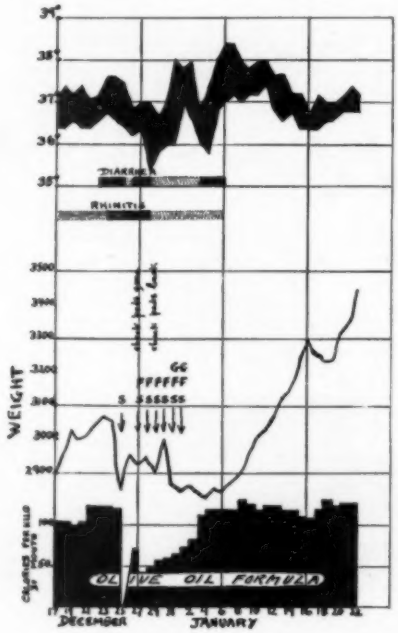

Chart 5.—Case 3 (A. K.).

been increased to 70 calories per kilogram. Although the infection had not yet worn itself out, and the diarrhea returned for a time when the calories were increased to 100 per kilogram, a marked and permanent improvement followed this very shortly.

Although the intravenous fat supplied only about one-third of the basal requirements here, we gained the impression that it had exerted a favorable influence. It is possible of course that the improvement was due to an increased tolerance for food given by mouth. On the other hand, when one considers that the state of the bowels was still abnormal and that the amount of food given by mouth was still small, it is rather difficult to attribute the change in general appearance and the return of fat pads to the cheeks to oral food alone.

If we scrutinize our clinical material for possible ill-effects from the treatment, several points come up for discussion. On several occasions a slightly subnormal temperature was noted following the injection; such temperatures are by no means uncommon in the type of subject we were dealing with, and the phenomenon was not constant enough to convince us that it was directly related to the treatment. On one occasion a transient glycosuria followed an injection; here again we doubt if the relation to the treatment was other than fortuitous. Four patients came to autopsy within forty-eight hours of a fat injection; in all these instances there was adequate cause for the fatal termination and no evidence that the fat had played a part in it. The capillaries of the lungs and of the other organs showed no aggregations of fat; a fatty liver was, however, found in two of the four cases. The occurrence of fatty liver in patients with nutritional disturbances due to infection is by no means rare, though an incidence of 50 per cent would hardly be expected. Some doubt exists as to the pathogenesis of this condition. Often there is no other evidence of liver pathology. The prevailing view[25] regards the liver as suffering from a functional incapacity to utilize the fat which it removes from the blood; fat therefore accumulates in the liver cells. Probably there are instances in which the fat-consuming function of the liver is only slightly impaired; in wasting conditions when the fat reserves are depleted and the blood fat diminished, such a liver might be able to handle a subnormal load without exhibiting fatty infiltration, whereas if the normal load were supplied artificially fat accumulation would promptly take place. If this be the case, one would expect that in clinical conditions likely to be associated with liver damage, the intravenous administration of fat might bring out an unusually high percentage of fatty livers.

Certainly there is no point in giving fat by vein to a patient whose liver is incapable of handling it; the administration of fat must be confined to those individuals whose liver performs this function normally. Up to the present time no clinical test has been developed to measure this function of the liver. We wish, however, to call attention to the current report of Nachlas,[26] who studied the lipemic curve after intravenous fat administration in experimentally produced hepatic lesions and found that this appeared to be an index of liver damage. It may be that this test will prove valuable in selecting cases in which benefit is to be expected from the intravenous administration of fat.

SUMMARY

1. It is possible to prepare fat emulsions that can safely be administered by vein.

2. Our experience confirms that of others, suggesting that these preparations are of value in parenteral feeding.

3. The possible limitations of their use are discussed.

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PRENATAL INFLUENCE IN RICKETS

I. Fetal Rickets

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ANTENATAL factors probably exert a considerable influence toward the rachitic tendency in the infant and may in some instances be of such magnitude as to cause the development of rickets in the fetus in utero. Maternal health and deficiency of essential elements in the diet during gestation, frequency of pregnancies, and inadequate exposure to sunlight are among the antenatal factors which appear to be important.

A. Maternal Health and the Diet During Gestation

It is known, primarily from experimental evidence, that parental nutrition is capable of exerting a definite influence on the occurrence of rickets in the offspring. Grant and Goettsch[1] found that in rats the diet of the mother was an important factor in increasing or decreasing the resistance of the young rats to the effects of diets that had been depleted of antirachitic factor alone. Grant[2] was also able to demonstrate that a lack of both vitamin D and minerals (calcium and phosphorus) in the diet of the mother rat produced rickets in the offspring which became manifest earlier and progressed faster than if the diet had been poor in the vitamin only. Somewhat similar findings were noted by Byfield and Daniels.[3] Toverud and Toverud[4] made a further contribution to this subject when they were able to create in the puppies of gravid dogs fed on a diet low in both minerals and the antirachitic factor an early and severe rickets far more pronounced than in puppies from mothers on an adequate diet.

The significance of early craniotabes and so-called "congenital osteoporosis" of the skull in relation to their much disputed association with rickets cannot be reviewed in detail, but some investigations carried out by Abels and Karplus[5] appear pertinent. These authors state that "soft skulls" (thin, soft, easily compressible bones with wide-open sutures and large fontanels) in newborn infants rest upon nutritional defects of the mother. They feel that "soft skulls" represent prerachitic changes and find that these young infants manifest an increased tendency to develop rickets later. Recent confirmation of this comes from Toverud[6] who not only maintains that newborn infants with "soft skulls" are born almost exclusively of women with a distinct deficiency in either diet or health but also that "hard skulls," in contradistinction, are born largely of mothers whose diet and health has been adequate and normal.

From the Department of Pediatrics, Harvard Medical School, and the Infants' and Children's Hospitals, Boston.

The Toveruds[4] and others[7] have found that where maternal health and diet have been sufficiently poor, the infants show fringy, poorly calcified epiphyses although Hess and Weinstock,[8] who previously encountered such changes, feel that they are equivocal and not necessarily pathognomonic of rickets. The latter authors, after the roentgenologic examination of the epiphyses of 250 newborn infants concluded that "although the incidence and severity of rickets may be influenced by improving prenatal nutrition, the disease is mainly of postnatal origin." While this statement is undoubtedly true, roentgenologic changes occur as a relatively late manifestation of rickets, and early roentgenologic examination may fail to disclose the disease.

B. Frequency of Pregnancy

As far as could be ascertained, frequency of pregnancy in the mother has not been given due consideration as a possible antenatal factor in the development of rickets in the infant. That this factor should have been neglected is surprising when one realizes the close correlation between osteomalacia and rickets and the effects that the advent of pregnancy brings in the former disorder. Recent work, particularly in China[9, 10] and India,[11, 12] indicates that these two disorders are due to a single cause, i.e., vitamin D deficiency. Both show the same relation to season and sunlight, the same response to cod liver oil, and similar chemical changes in the blood of patients. Histologically the bones of osteomalacia give the appearance of rickets as it might be expected to appear if involving the adult bone. Miles and Feng[13] have shown that osteomalacia is frequently precipitated by the gravid state and becomes more acute during the later months of pregnancy. Not infrequently an initial appearance is delayed until parity has become multiple, and with each subsequent pregnancy the disease becomes more severe. According to Hess,[14] one observer has gone so far as to state that in the course of any normal pregnancy the bones undergo mild osteomalacic changes of subroentgenologic character, due to an abnormal intensification of the physiologic drain of inorganic salts, which takes place during gestation. This work, adds Hess, has never been refuted or confirmed.

Hess and Matzner[15] found that while the inorganic phosphorus of the blood of pregnant women may be approximately normal, the calcium is reduced at term. Toverud and Toverud[4] have demonstrated that women (on an average Norwegian diet) often show a negative calcium and phosphorus balance during gestation and, less frequently, during lactation. They likewise have shown that the calcium content of breast milk may become subnormal. Even in the presence of an adequate diet during pregnancy, Jundell and Magnusson[16] believe that the administration of cod liver oil to the mother raises the inorganic phosphorus content of umbilical cord blood. Working on rats, Grant and Goettsch[1] determined that under ordinary circumstances

rickets does not develop readily in the offspring of well-nourished rats when a partial lack of the antirachitic vitamin is the only deficiency in the diet. When these same rats on the same diet are forced into repeated pregnancies in the absence of sunshine, the later litters exhibit a strong tendency to early and severe rickets. A clinical example of the effect of repeated pregnancies is well illustrated in a case of severe rickets reported by Jungwirth.[17] In this instance the mother had undergone eight pregnancies in a short time, and while the first five siblings were quite normal, the last three all had rickets. Each case was more severe than its predecessor. A case recently studied in this clinic that will be reported in detail elsewhere represents another example. The mother had five children in nine years. Three of them showed no evidences suggestive of rickets, but the two younger children both had florid rickets, the last born showing extensive involvement at the age of two months.

C. Effect of Sunshine on Mother and Fetus

That insufficient exposure of the mother to the actinic rays of the sun may play a not inconsiderable part in the causation of early rickets is evidenced by an extensive survey conducted by Hutchison and Sha[18] in India. They learned that 25 per cent of the infants from well-to-do mothers who practiced "purdah"* had definite signs of rickets, whereas only 5 per cent of the children from the lower caste Hindus had evidence of the disease. The mothers of this latter group do not observe "purdah" and get an abundance of sunshine. Further enlightenment is to be had from the studies of Grant, which have already been discussed.

FETAL OR CONGENITAL RICKETS

Antenatal factors, while undoubtedly capable of exerting an influence toward a rachitic tendency in the infant, are rarely of sufficient magnitude to create rickets in utero. The occurrence of the disorder in the unborn child was for many years not countenanced by many workers, who based their conclusions largely on the investigations of Schmorl.[19] He concluded, because of failure to find histologic evidence of rickets in an examination of over one hundred full-term and prematurely born infants coming to necropsy, that fetal rickets did not exist. The series of cases would appear rather small to justify such a conclusion.

Occasional reports of congenital rickets have appeared. Most of these reports have lacked the important essential of histologic corroboration. It was not until Maxwell began his investigations in China that fetal rickets was definitely established as an entity. Several years ago he and Miles[9] called attention to the incidence of

*A form of religious seclusion practiced by high caste Hindu and Mohammedan women.

osteomalacia in certain districts of China and showed that the diets of the mothers afflicted with this disease were deficient in calcium, phosphorus, and vitamin D. In 1930 Maxwell and Turnbull[20] presented evidence suggestive of the existence of fetal rickets in infants born of osteomalacic mothers. Two cases were cited: in one of these the evidence was afforded only by roentgenogram, while in the other the badly preserved condition of the bones detracted to some extent from the value of the material presented.

In 1932 Maxwell and his coworkers[10] established beyond any doubt that rickets does occur in utero. A detailed report was presented of a Chinese woman, aged thirty-eight years, who had been on a starvation diet (consisting of two daily meals and containing no meat or animal fat) for three years and had suffered from the pains of osteomalacia for two years. At the time of delivery she had a hypocalcemia (7.38 milligrams per cent), and the infant, weighing 2,835 gm., showed a marked rosary and Harrison's grooves. Radiograms of the infant disclosed rachitic-like changes of the long bones that were later verified by histologic examination.

As Turnbull points out, there is no histologic distinction between osteomalacia and rickets, but we do not definitely know that the two conditions are identical. Thus, "if osteomalacia differs causally from rickets, then these infants are the osteomalacic offspring of osteomalacic mothers."

REPORT OF AN ADDITIONAL CASE OF FETAL RICKETS

While osteomalacia is encountered frequently in China and India and is common in certain parts of Central Europe, it is seldom recognized in America. As a consequence, one would hardly expect to see congenital rickets in this country. Nevertheless an additional case, the fourth to be reported and the second proved case, has been encountered in Massachusetts.

Baby C, a white female infant two days of age, was admitted to the hospital because of bleeding from the nose and mouth.

The mother, thirty-two years old, had been in an extremely poor nutritional state throughout pregnancy. She had been vomiting severely for weeks and had been able to retain little food. During the latter months of pregnancy she suffered from hypertension and at the time of delivery had albuminuria and marked secondary anemia.

The baby was delivered at full term by podalic version and breach extraction. The immediate postnatal condition of the infant was good, and the birth weight was said to have been about 7 pounds and 8 ounces. Approximately eight hours after birth, however, spontaneous bleeding from the nose and mouth occurred. On the following day an attending physician administered 25 c.c. of whole blood intramuscularly without effect. The condition of the infant became progressively worse; repeated hematemesis took place; respiratory irregularity developed; and death occurred on the second day of life.

Radiograms of the costochondral junctions disclosed a marked flare and irregular metaphyseal cupping.

Abstract of Autopsy Protocol

Necropsy was performed four hours postmortem. The body was that of a well-nourished and developed white female infant whose general appearance was not unusual except for a marked rosary of rachitic type. There was gross hemorrhage into the scalp, alimentary tract, and into the retroperitoneal tissue of the right iliac

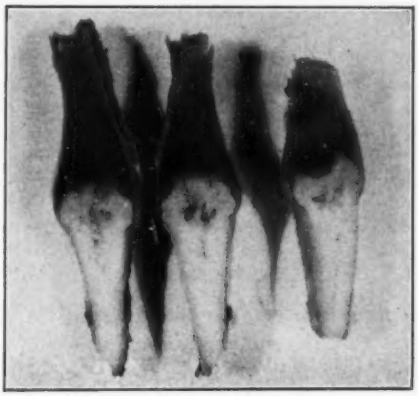

Fig. 1.—Photograph of split sections of three ribs showing the costochondral junctures. Note the irregularity of the metaphyseal lines, overproduction of cartilage, and distortion and swelling of the constochondral junctions.

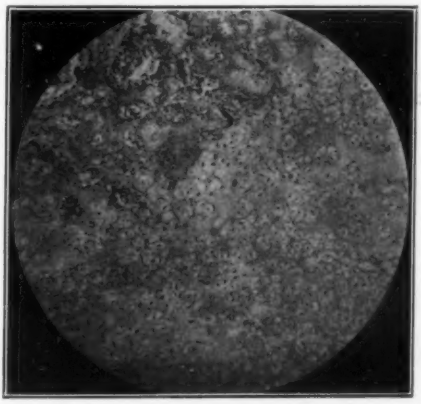

Fig. 2.—Photomicrograph of section of rib showing an area in the region of the metaphyse-epiphyseal junction. Note overgrowth and disorganization of columns of cartilage, evidences of lack of normal cartilage, invasion and bone formation, excess osteoid tissue, and irregularity of metaphyseal line. (Hematoxylin and eosin, ×90.)

region. In addition, there were petechial hemorrhages in the thymus, heart, lungs, and bladder, with congestion of the spleen, liver, kidneys, adrenals, and brain.

The most interesting findings were those in the bones. Gross inspection revealed a marked thickening of the costochondral junctions (Fig. 1). The primary zone of ossification was slightly irregular and moderately thickened. The periosteum and perichondrium were not remarkable, and there was no subperiosteal hemorrhage. A

striking feature was the marked pallor and density of the trabecular bone, particularly in the vertebrae.

Eight sections of bone were made, four of costochondral junction and four of vertebrae. Microscopic examination of the latter showed well-developed trabecular bone containing the usual islands of cartilage. The interstices were well filled with active hematopoietic cells, and there was a narrow, regular osteochondral junction. Histologic sections of the costochondral junction, however, showed a marked deviation from normal, principally due to a much thickened, widened, and very cellular preparatory zone of cartilage (Fig. 2). The junction between bone and cartilage was irregularly convex toward the diaphysis. The cartilage showed no evidence of preliminary calcification and had been irregularly invaded by both marrow and perichondrial vessels. There were small amounts of osteoid tissue. The bone spicules were thin but numerous and calcified. Many giant cells were seen on the periosteal surface of the cortical bone on the inner aspect of the ribs. These were less numerous on the surface of the spicules. Osteoblasts were abundant, and there was a moderate amount of active marrow.

Anatomical diagnosis: hemorrhagic disease of newborn; fetal rickets.

SUMMARY

A review of the literature on prenatal influence in rickets indicates that maternal health and diet are outstanding etiologic factors and that frequent pregnancies and lack of exposure to sunshine may be contributory factors which exert an influence on the development of rickets in the very young infant.

A case of fetal rickets established by roentgenograms of the bones and confirmed by histologic examination is reported. The rachitic process in the infant was apparently due to severe malnutrition in the mother.

I am indebted to Dr. Sidney Farber, of the Department of Pathology of the Harvard Medical School, for the study of the pathologic material.

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PRENATAL INFLUENCE IN RICKETS

II. Early Postnatal Rickets and Florid Rickets With Multiple Fractures

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IN A previous paper attention was directed to antenatal influence in rickets and to the occurrence of fetal rickets. Some of the important prenatal factors were discussed and a case of fetal rickets was reported.[1]

The purpose of this study is to ascertain the effect of maternal influence on the development of certain other forms of rickets in the infant. The study is based upon a survey of 400 cases of active rickets.

A. EARLY POSTNATAL RICKETS IN THE INFANT BORN AT TERM

Investigators have rather uniformly agreed that rickets is a rarity under three months of age, and yet the literature yields little as to the actual incidence in this age group. Hess[2] states that rickets begins about the third month and ends about the eighteenth month. Holt and McIntosh[3] mention the period from the fourth to the eighteenth month and go on to say that the disease is rare before the third month and after the second year. Schmorl[4] in 1909 conducted a pathologic study on 365 cases of rickets examined at autopsy and found histologic evidence of the disease in twenty infants under three months of age, an incidence of 5.5 per cent. Four of the patients were two months old, and the others were all between two and three months old. It is well known that premature infants and twins are susceptible to early and severe rickets. Ylppo[5] has observed rickets in a premature infant at the age of six weeks. The youngest patient with rickets described in this country was an infant thirty-four days old, reported by Dunham,[6] and while this baby was allegedly born prematurely, its birth weight was 3,260 gm.

Rickets in the Infant Born at Term.—In an attempt to determine the actual incidence of early rickets, and to investigate possible etiologic factors of significance, 400 cases of rickets seen in this clinic over a period of the past nine years have been reviewed. All of these were in an active phase of the disease, and in each instance clinical diagnosis was corroborated by roentgenographic examination and chemi-

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cal analysis of the blood. Only patients with abnormally low phosphorus have been included in this survey.

In this series of 400 it was found that thirty-two cases, or 8 per cent, were aged three months or younger. Of these, the youngest was a full-term infant of thirty-five days. Fourteen of the thirty-two were under two months of age, and eighteen infants were from two to three months old.

When one considers the generally accepted rarity of rickets in the first three months of life, it is surprising to find that 8 per cent of the cases of rickets developed in this age group. Exactly half of the infants were the result either of premature birth or of twin pregnancy. The other sixteen infants were all born at full term.

Thus among 400 cases of rickets 4 per cent (sixteen cases) occurred in full-term infants under three months of age. Among these, 1.75 per cent were less than two months old, and 2.25 per cent were in their second or third month of life. None of the sixteen had a birth weight of less than 6 pounds and 12 ounces, which is well above the figure arbitrarily accepted as one of the indices of prematurity. The average weight at birth was 7 pounds.

Comment.—With only three exceptions this group of full-term infants presented on admission an excellent state of nutrition and had shown consistent gains in weight since birth. Most of them appeared healthy, and hospitalization was usually requested because of mild respiratory infection or convulsions from an associated tetany. The association of tetany with rickets in these very young infants is worthy of note. A recent analysis by Guild[7] of 293 cases of tetany from the Harriet Lane Home disclosed an incidence of 7½ per cent in patients under three months. Since infantile tetany almost always develops on the basis of a previous rickets, the close parallelism between this figure and the 8 per cent incidence of rickets found in this series for the same age group is of interest. The youngest case of tetany in the recent literature was reported in a nine-day-old infant by Small.[8]

It is known that "roentgenologic rickets" indicates a fairly advanced stage of the disease, for in 1928 Wimberger[9] demonstrated that the interval between the first histologic rachitic change and the first radiographic change is "certainly as long as several weeks." When one recalls that almost half of this full-term group showed roentgenologic evidence of the disease prior to the second month, it at once becomes evident that in them the disorder must have had its incipiency in the very early weeks after birth.

Turning to an analysis of possible contributory factors to the development of such an early rickets it is seen that prenatal influence may be of importance (Table I). An investigation of maternal health and diet during pregnancy was not quite as satisfactory as might be

TABLE I

CASE ANALYSIS OF ETIOLOGIC FACTORS IN FULL-TERM INFANTS WITH ACTIVE RICKETS UNDER THREE MONTHS

	ANTENATAL FACTORS				POSTNATAL FACTORS				
CASE	MATERNAL DIET	MATERNAL HEALTH	YEARS MARRIED	NUMBER OF CHILDREN	SEX	NATIONALITY	FEEDING	COD LIVER OIL	MONTH
1	Unknown	Poor	8	6	F	Irish	Breast	Adequate	August
2	Deficient	Poor	9	5	F	Irish	Breast	None	October
3	Unknown	Unknown	Unknown	Unknown	M	American	Artificial	None	February
4	Good	Good	7	5	F	Scotch	Breast	None	September
5	Unknown	Unknown	Unknown	Unknown	M	American	Breast	None	November
6	Unknown	Unknown	9	6	M	Irish	Breast	None	March
7	Deficient	Poor	5	3	M	Italian	Artificial	Inadequate	September
8	Unknown	Unknown	17	9	F	German	Breast	None	April
9	Unknown	Unknown	6	5	M	Scotch	Breast	None	January
10	Unknown	Unknown	Unknown	Unknown	F	Scotch	Artificial	None	March
11	Unknown	Unknown	13	6	F	American	Breast	None	October
12	Good	Good	10	8	M	Irish	Breast	None	June
13	Unknown	Poor	4	2	F	Italian	Breast	Adequate	January
14	Unknown	Unknown	Unknown	Unknown	M	Irish	Artificial	None	December
15	Unknown	Unknown	8	5	F	American	Breast	None	February
16	Deficient	Poor	2.5	2	F	German	Breast	None	May

desired because relevant data could be accumulated in only seven of the sixteen cases. In these, however, the results were striking. Only two of the mothers had been healthy and had received an adequate diet. Five of the women had a rachitogenic diet, poor health, or both. Their diets consisted largely of fruits and vegetables with no meat, no milk, and no eggs. Impairment of health was so extreme that confinement indoors had resulted; in at least three cases there was practically no exposure to sunlight during the latter months of pregnancy. Frequent pregnancies were a prominent feature in the maternal background. Seventy-five per cent of these mothers had five or more children in nearly as many years. They were women who nursed their young, usually for a prolonged period. Thus, it may be seen that in almost every case there was at least one, and often a combination of maternal factors, which might influence the growth and development of the infant. Each of these factors, poor health, deficient diets, frequent pregnancies, absence of exposure to sunshine, and prolonged lactation, may exert an influence on the infant to impair bodily nutrition, alter metabolism, and particularly to create a depletion of maternal and fetal calcium and phosphorus.

Consideration of postnatal factors yields little information with respect to the causation of early rickets. Nationality, sex, season, and infection were not contributory. The only points seemingly worthy of note were moderately rapid weight gains and an absence of cod liver oil from most of the infant dietaries. An actively growing infant, who is not given cod liver oil or a substitute, will usually show some degree of rachitic change eventually unless there is frequent exposure to sunshine. It is to be recalled, however, that 75 per cent (twelve cases) of the babies under consideration were breast fed. In view of the relative infrequency of rickets in the breast-fed infant, it seems likely that the development of early postnatal rickets was dependent largely upon nutritional defects in the mother. In the light of present knowledge the mechanism of this relationship cannot be definitely stated although it may well be much the same as that which probably obtains in the premature infant. The latter has a deficiency of stored calcium and phosphorus, due presumably to an immature maturation incident to an early termination of intrauterine life. The full-term infant born of a mother impoverished nutritionally also has a lack of stored calcium and phosphorus, but this occurs as a result of impaired metabolism on the part of the mother. Several years ago Hess and Matzner[10] decided that the percentage of inorganic phosphorus and calcium in the circulating blood of the newborn bore no relationship to the occurrence of rickets during the first year, but some recent work by Toverud and Toverud[11] may be of significance. Working on young puppies born of dogs placed on rachitogenic diets, they were able to produce an early and extensive rickets far more

pronounced than in control puppies born from nutritionally sound mothers. While these puppies at birth revealed no histologic or roentgenologic evidence of rickets, a chemical analysis of the bones disclosed a distinct lowering in the calcium and phosphorus content throughout the skeleton.

In the series of cases reported the nutritional defects of the maternal organism were not of sufficient magnitude to produce an actual rickets in the infant prior to birth. Instead, a moderately defective nutritional state possibly induced a "congenital tendency" which was elaborated primarily through an impaired mineralization of fetal bone. Changes incident to the great growth stimulus cause, following birth, an increased depletion of calcium and phosphorus, and the "congenital tendency" becomes the actual disease.

B. SEVERE INFANTILE RICKETS WITH MULTIPLE FRACTURES

Cases of rickets are encountered which manifest an extremely severe form of the disease with marked osteoporosis that results in spontaneous multiple fractures. Excluding such factors as race and possibly an increased disposition to rickets sometimes in evidence throughout certain families, one is usually at a loss to explain these types of the disease. A review of the literature shows a surprising dearth of material on the subject. The association of fractures with rachitic bone changes has been reported in this country by Dunham,[6] Hess,[2] and Park and Howland.[12] The last named authors describe a series of negro children with advanced rickets and severe thoracic deformities; some of these patients showed multiple fractures of the extremities. Cases have been recorded elsewhere by Lereboullet and Chabun,[13] Steiner,[14] and Jungwirth.[15] Apparently as age increases, the incidence of fractures becomes higher. In the late rickets (rachitis tarda) of childhood and the osteomalacia of puberty and pregnancy, fractures become very common. Hutchison and Stapleton[16] have reported a number of cases of this type from India. The only case of a rachitic patient with fractures under three months of age that could be found was Dunham's case of rickets in an infant thirty-four days old. This baby had multiple fractures of the ribs.

CASE REPORT

A case of flagrant rickets that showed multiple fractures at the age of two months was recently studied in this clinic. The case is thought to be sufficiently unusual to warrant a report in some detail because of the extreme rarity of multiple fractures at this age and because of the possible influence of maternal factors on the development of the disease.

G. M., a four-month-old female infant from a poor Italian family, entered the hospital on Sept. 12, 1933, with a complaint of "failure to gain." The mother was twenty-five years old; she had been married for nine years, and this was the fifth child. Her health had been poor for several years, and with the onset of this pregnancy it became much worse. There was a constant nausea present; throughout pregnancy she ate little except cooked vegetables, occasional small amounts of raw fruits (oranges and apples) and soup. Meats, milk, and eggs were entirely excluded from this self-imposed diet. A vaginal discharge had been present for some months and during the height of pregnancy she developed severe pains in her legs and joints diagnosed as "gonorrheal arthritis." These became of such severity that during the latter months of confinement she was unable to descend stairs and was forced to remain in a room that received little sunlight. Weakness was an outstanding feature. Severe dental caries developed. Following a full-term, difficult delivery, there was considerable spontaneous improvement of her pain, and subsequent ultraviolet irradiation created a prompt remission. The family history was of further interest. Three of the four siblings were in good health, but the youngest, aged two years, showed evidence of an advanced rickets with a large square head, prominent frontal bosses, rachitic rosary, extensive bowing of the legs, and epiphyseal enlargement.

The patient weighed 6 pounds and 4 ounces at birth, and her immediate postnatal condition was good. She was placed on a modification containing dextrimaltose, milk, and water. This was taken with avidity, and, while the infant seemed in good condition, she was unable to gain consistently. Orange juice was begun at one month and administered thereafter in adequate amounts. During the ensuing weeks the infant continued in uneventful fashion until she was two months old. At this time the mother detected a swelling of the "front of the left shin bone." This was only slightly tender, seemed quite hard, and in no way curtailed the baby's activities. A few days later there occurred a single generalized convulsion. Cod liver oil was then begun in daily teaspoon amounts but after one month it was discontinued because of occasional attacks of diarrhea. The baby still showed no tendency to gain, and finally at the age of four months she was brought to the hospital for investigation.

On admission, examination disclosed an underdeveloped and markedly undernourished, hypertonic female infant who weighed 7 pounds and 5 ounces. She appeared chronically ill; color was an ashen pallor, and skin turgor was poor. The head was of square configuration with prominence of supraorbital bosses. There was no demonstrable craniotabes. A rosary of rachitic type was present, and a beginning Harrison's groove was detectable. The abdomen was quite protuberant and the splenic edge could be palpated 2 cm. below the costal margin. Epiphyseal enlargement was not evident, but over the anterolateral aspect of the left tibia a rather diffuse swelling could readily be seen. This was hard in consistency, seemed to be contiguous with the bone, and was not tender to manipulation. There was frequent spontaneous movement of all extremities without apparent discomfort.

An anemia of hypochromic type was found; serum calcium content was 7.7 mg. per 100 c.c.,* and the inorganic phosphorus was 4.5 mg. per cent.† A plasma phosphatase content of 1.3 units per cubic centimeter‡ was indicative of advanced active rickets.[17] Other data, including serum protein, nonprotein nitrogen, and renal function tests, were within normal limits. Mantoux tuberculin tests, run up

*Calcium determination by method of Fiske—normal range during first year from 9 to 12mg. per cent.

†Phosphorus determination by method of Fiske and Subbarow—normal range during first year, from 4.5 to 5.5 mg. per cent.

‡Phosphatase determination by method of Kay—normal range for infants under one year from 0.10 to 0.27 units per cubic centimeter.

to 100 mg. of old tuberculin, produced no reaction. The Wassermann, Hinton, and Kahn reactions on both parents and baby were negative.

Roentgenograms (Sept. 13, 1933) showed multiple fractures, including the left clavicle, the seventh left rib anteriorly, the left radius, left ulna, and the right radius. There were also two fractures of the left tibia and two of the left fibula. These were all surrounded by a moderate amount of callus formation. There was an extreme degree of generalized osteoporosis, and the metaphyseal margins were irregular and defectively calcified (Fig. 1).

The infant was immediately placed on a vigorous antirachitic regimen consisting of liberal amounts of a halibut liver oil preparation fortified with viosterol. Ultraviolet irradiation was given. Reexamination of the long bones two weeks after entry (Sept. 26, 1933) showed definite improvement, characterized by an increase in the amount and density of the callus around the fractures. Likewise, the osteoid at

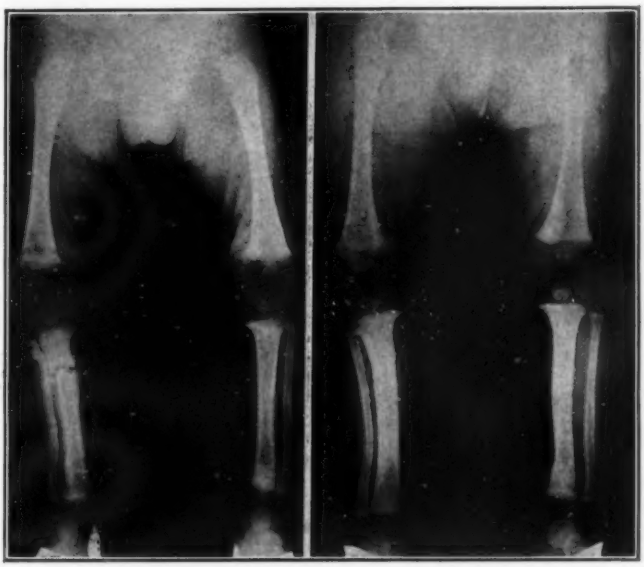

Fig. 1. Fig. 2.

Fig. 1.—A film of the lower extremities taken Sept. 13, 1933. Note the generalized osteoporosis, the irregular metaphyseal margins, and multiple fractures. There are two fractures of the left tibia and two of the left fibula.

Fig. 2.—Roentgenogram at time of discharge, Nov. 14, 1933. This illustrates complete healing of the infractions in good position with no remaining evidence of previous existence. Calcification has become almost normal, but slight rachitic changes are still extant.

the ends of the long bones showed increased calcification. Serum calcium at this time had risen to 12.4 mg. per cent and phosphorus to 5.9 mg. Another film taken two weeks later (Oct. 11, 1933) disclosed well-calcified metaphyses, and all of the fractures almost united. Six weeks after admission the fractures were well healed, and the only evidence of their previous existence was a small amount of unresolved callus in the left tibia. Upon discharge two months after entry (Nov. 16, 1933) the radiograph demonstrated complete effacement of all fracture lines although there were some slight rachitic changes still present (Fig. 2). Serum calcium was then 10 mg. per 100 c.c., and phosphorus, 5.7. A plasma phosphatase of 0.51 units

per cubic centimeter was further evidence that healing was as yet not complete. Throughout her stay there was marked general improvement and a weight gain of almost five pounds in two months.

That osteomalacia was present in the mother during the latter months of her pregnancy seems probable. A rachitogenic diet, frequent pregnancies, poor health, and an insufficient exposure to sunshine are all etiologic factors to the development of this disorder. The disease is further suggested by the extreme weakness and severe joint pain, which are outstanding symptoms of osteomalacia. At the time she was seen, however, this diagnosis could not be confirmed. A radiograph of her extremities taken six months postpartum (Nov. 16, 1933) showed nothing of note, although this is not surprising in view of the fact that her diet since delivery had been normal. She had also received over a month of intensive ultraviolet light therapy, which would contribute to further healing. A request for calcium and phosphorus determination on the mother was refused.

This case, in several respects, resembles the one reported by Dunham. The mother of that baby had undergone seven pregnancies, had been exposed to very little sunlight, and her diet had been very deficient. During the latter months of pregnancy weakness and pain in the legs developed. X-rays disclosed considerable rarefaction of the bones; it was likely that she had osteomalacia.

A SURVEY OF 400 CASES OF ACTIVE RICKETS WITH AN ANALYSIS OF CASES WITH FRACTURES

Of the four hundred cases of rickets surveyed by the author, fractures occurred in fourteen instances; an incidence of 3.5 per cent. Nine of the patients who developed fractures were full-term infants and the remainder were either premature infants or twins.

The age incidence in this group closely followed that usually seen in rickets, with an average range of from six to fifteen months. The youngest was two months old, and the oldest, twenty-six months. Only two cases were found in infants under three months of age.

The patients with severe rickets associated with fractures entered the hospital with a chief complaint of "failure to gain" or "cough." Almost without exception they presented extreme degrees of malnutrition and underdevelopment. Severe respiratory infections were frequent; and the mortality in the group was 29 per cent, death occurring from bronchopneumonia.

COMMENT

The etiologic factor in the causation of severe rickets with fractures cannot be definitely stated. Postnatal factors did not seem to be outstanding. (Table II.) Sex, season, and nationality were hardly worthy of connotation. Five of the fourteen infants were breast fed;

TABLE II

CASE ANALYSIS OF ETIOLOGIC FACTORS IN INFANTS WITH FRACTURES

	ANTENATAL FACTORS				POSTNATAL FACTORS				
CASE	MATERNAL DIET	MATERNAL HEALTH	YEARS MARRIED	NUMBER OF CHILDREN	SEX	NATIONALITY	FEEDING	COD LIVER OIL	MONTH
1	Unknown	Unknown	4	2	M	Irish	Breast	None	December
2	Unknown	Poor	11	7	M	Italian	Artificial	Adequate	October
3	Deficient	Poor	5	3	F	American	Artificial	Adequate	February
4	Unknown	Unknown	8	6	M	Greek	Breast	Inadequate	April
5	Unknown	Poor	?	?	F	American	Artificial	None	July
6	Good	Good	1	2	F	Irish	Artificial	None	February
7	Deficient	Poor	9	5	F	Italian	Artificial	Inadequate	September
8	Unknown	Unknown	6	5	M	Italian	Breast	Adequate	August
9	Unknown	Poor	3	1	F	Scotch	Artificial	None	July
10	Unknown	Unknown	?	?	M	Greek	Artificial	Adequate	March
11	Deficient	Poor	13	8	M	Irish	Breast	Adequate	April
12	Unknown	Unknown	?	?	F	American	Artificial	Adequate	October
13	Deficient	Poor	6	4	M	Portuguese	Artificial	None	March
14	Unknown	Unknown	9	6	F	Italian	Breast	None	January

the others all had adequate artificial formulas with but three exceptions. Forty-three per cent of these babies received cod liver oil or a substitute in amounts ordinarily sufficient to prevent rickets. Infection was a prominent feature in the majority of cases but may have been the result rather than a predisposing cause of the development of rickets.

Accurate maternal history could be obtained in eleven of the fourteen cases. Fifty-five per cent, or six cases, had a history of five or more pregnancies in rapid succession. Data concerning the mother's health and dietary were ascertained in eight instances. Only one mother was definitely known to have had both an adequate diet and good health. In this case the infant was born prematurely and was a twin so that the florid rickets and multiple fractures seen in this baby are more readily understood. Four mothers had very poor health and diets that were definitely deficient, while in three others health was impaired but no details of the diets could be elicited. In two cases in which the maternal health and diet were exceptionally bad, the infants, in addition to multiple fractures, had thoracic and spinal deformities. These cases were somewhat similar to those reported by Park and Howland.[12] Grant[18] describes cases in young rats born of mothers with particularly defective diets, who developed extensive osteoporosis, multiple fractures, thoracic deformities, and kyphosis.

Calcium and phosphorus determinations in these cases with multiple fractures differed in no essentials from the figures obtained in usual cases of rickets. By roentgenogram all cases showed metaphyseal irregularity and cupping, but the outstanding feature in each case was a generalized osteoporosis of extreme degree. This characteristic is of interest in regard to an observation made by Toverud and Toverud.[11] They had placed pregnant rats on a diet markedly deficient in calcium, but otherwise adequate, and found that the young of these mothers showed an extensive osteoporosis with multiple fractures but relatively little actual rachitic change in the metaphyses. One cannot postulate that the same mechanism prevailed in these infants with multiple fractures. However, there were antenatal factors present in a large number which were capable of exerting an influence on fetal metabolism. It would be most interesting if one could know the age at which rickets first developed in these babies who subsequently progressed to the stage of multiple fractures. It seems likely that a considerable portion would have shown rickets in the early months of life.

SUMMARY

A review of literature on early postnatal rickets and rickets with multiple fractures, together with a survey of 400 cases of active rickets and the determination of the incidence of early rickets and of rickets

with multiple fractures, permits an analysis of possible factors contributory to the development of these two forms of the disease.

It is suggested that early postnatal rickets and florid rickets with multiple fractures may result from an insufficiency of stored skeletal calcium at the time of birth incident to nutritional and metabolic defects on the part of the maternal organism.

A case of early infantile rickets with multiple fractures is reported.

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2000 VAN NESS AVENUE

A RARE AND PECULIAR FORM OF ACUTE INTERSTITIAL PNEUMONIA

Report of Eight Cases

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A RARE and peculiar form of acute interstitial pneumonia was discovered at autopsy in eight infants and children treated in the Jewish and Mount Sinai Hospitals during 1931 and 1932. Four of the cases were on the writer's service at the Jewish Hospital; two were on his service at the Mount Sinai Hospital; and two were on the service of Dr. Harry Lowenberg at the Mount Sinai Hospital.

CASE REPORTS

Case 1.—J. L., a five-month-old colored male infant, was admitted to the Jewish Hospital on Feb. 20, 1931, with dyspnea and grunting expiration which had developed the day previous, with a slight cough of several days' duration, and with fretfulness that had existed for a week.

The family history and the past medical history were negative.

The baby appeared very sick. The temperature was 103° F.; the pulse was imperceptible; and the respirations were about 80 and very shallow. Some cyanosis and playing of the alae nasi were present. There was no nuchial rigidity and no Kernig's sign. The lungs showed some impairment at the apices. The breath sounds were harsh and rough throughout, but there were no râles. The abdomen was slightly distended. A diagnosis of bilateral bronchopneumonia was made. A mustard plaster was applied over the whole chest. The child was given a colonic irrigation of a 5 per cent solution of sodium bicarbonate. Whisky, potassium citrate, and aromatic spirits of ammonia were administered by mouth. Two and three-quarters hours after admission the baby died.

The autopsy was performed by Dr. S. Levine, the surgical pathologist to the hospital, who made a diagnosis of bronchopneumonia, septicemia, and cloudy swelling of the liver and kidneys.

There was no effusion in either pleural cavity. The parietal pleura was studded with small pinpoint petechiae. The lungs presented numerous circumscribed areas of consolidation, sharply outlined and of increased consistency, sinking on being immersed in water. Very little pus could be expressed from the areas involved. The tracheobronchial glands were not enlarged.

The histologic examination was made by Dr. B. A. Gouley, the hospital pathologist. The lungs showed nonsuppurative pneumonitis. There was marked engorgement of the capillaries and infiltration of epithelioid cells throughout. The pleura was thickened by hemorrhage and edema. The alveoli contained fibrin and desquamated epithelium cells but no polymorphonuclear exudate. In many places they were empty. Associated with the interstitial thickening there was a certain

From the pediatric wards of the Jewish and Mount Sinai Hospitals, Philadelphia.
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degree of collapse, more marked in some fields than in others. The bronchi seen showed no definite pathology. This acute nonsuppurative interstitial pneumonitis was identical with that seen in rheumatic fever. Small foci of necrosis occupied the interstitial infiltration.

Culture of the heart's blood showed a short-chain, gram-positive diplococcus and gram-negative diplococci (*B. coli*). It was impossible to isolate the organisms.

CASE 2.—E. J., a four-month-old negro girl, was admitted to the Jewish Hospital on Apr. 8, 1932. The baby had had a cold for a week with running nose and cough. On the day preceding admission, the mother noticed the child was having difficulty in breathing and brought her to the accident ward where tentative diagnoses were made of (1) enlarged thymus, (2) laryngeal diphtheria, (3) foreign body in the air passages, or (4) edema of the larynx secondary to upper respiratory infection. After roentgen ray treatment over the thymus gland, breathing became easier. X-ray examination failed to reveal a foreign body but disclosed a small consolidation of the right lung. The trachea and larynx appeared clear and not displaced. Throat smear showed diphtheroids, and throat culture showed *Staphylococcus aureus.*

The child was sent home but did not improve and next day was admitted to the ward.

The child seemed very ill and had laryngeal stridor. The laryngologist and bronchoscopist at first regarded the case as one of laryngeal stridor but later decided against a definite laryngeal obstruction, regarding the dyspnea as due to the pulmonary condition. The face and lips were extremely cyanotic and ashy in color. There was no nucheal rigidity. The heart sounds were very rapid but of good quality. There was no murmur. The lungs showed evidence of slight consolidation posteriorly below the angle of the right scapula. The abdomen was moderately distended but not rigid. There was a slight umbilical hernia. No organs or masses were palpable. There was no eruption.

Throat smears on April 9 and 11 were negative for diphtheria bacilli. Throat culture on April 9 showed *Staphylococcus aureus.* Nasal culture on April 11 was negative for diphtheria bacilli and contained *Staphylococcus aureus* and *Bacillus proteus.*

The baby was placed in an oxygen tent with her head hyperextended, in which position she breathed more easily. An intraperitoneal injection of 200 c.c. of Hartmann's solution, hypodermoclysis of 500 c.c. of normal saline solution with 50 c.c. of a 50 per cent solution of glucose and an asafetida enema were given. A rectal tube was inserted. The temperature, which was 101.8° F. on admission, dropped to 101° and then rose steadily to 105.8°. Eight hours after admission cyanosis and laryngeal stridor were no longer present, and two and a half hours later the baby died.

The autopsy and histologic examination were made by Dr. B. A. Gouley, who made a diagnosis of lobar interstitial and alveolar pneumonia. In the right upper lobe a firm, greyish red pneumonic consolidation, the size of a 10-cent piece, was found occupying the lower half of the lobe. A similar but smaller lesion was found in the adjacent portion of the lower lobe and in the periphery of the left upper lobe.

Section of the lung showed the same type of very densely cellular lobar pneumonia that had been noted in other babies the preceding winter. The cellular infiltration was heavy, but in addition a much greater percentage of polymorphonuclear cells in the alveolar exudate than in the other cases was noted. Curiously, most of the polymorphonuclear cells were broken up. A few alveoli contained

chiefly fibrin and red blood cells, and in some fields the interstitial involvement, and the variety of cells—endothelial, epithelioid, and polymorphonuclear—was striking.

Postmortem smears of the lung showed many pneumococci, some pus cells, and no tubercle bacilli.

CASE 3.—M. J., a negro girl, seven months old, was admitted to the Jewish Hospital on Apr. 22, 1932.

The family and past medical histories were negative.

The child had had a cold for three weeks and had been grunting most of the time.

The child appeared acutely ill and very toxic. She had a square head and a patent anterior fontanel; the sutures were not all closed. The respirations were very shallow and rapid, with grunting expiration. There was no movement of the alae nasi. Retraction of the interspaces and of the epigastrium was observed during inspiration. A rachitic rosary was present, and the wrists and ankles were enlarged. The heart was enlarged above and to the left. There was dullness on the right side anteriorly below the second rib, in the axilla below the third rib, and posteriorly above the third rib. On the left there was slight dullness over the whole chest anteriorly, marked dullness over the whole chest posteriorly, and slight dullness above the fifth rib in the axilla. Breath sounds were exaggerated on the right posteriorly, and there was slight bronchial breathing on the left posteriorly with crepitant râles at the base. The tonsils, pharynx, and both eardrums were slightly injected.

The hemoglobin was 40 per cent, and the red blood cell count was 3,150,000 with slight achromia, slight anisocytosis and occasional poikilocytosis. The leucocytes were 6,500 with 55 per cent neutrophiles and 45 per cent lymphocytes. The temperature, which on admission was 103.6° F., dropped to 101.4° and then rose to 104.2°.

The baby was given a course of calomel, followed by milk of magnesia, an asafetida enema, tincture of digitalis, whisky, and sodium citrate. Eight hours after admission 7½ grains of quinine and urea hydrochloride were injected intramuscularly. Fifteen minutes later the baby died.

The autopsy and histologic examination were performed by Dr. B. A. Gouley, who made a diagnosis of interstitial lobar pneumonia.

The internal examination showed pneumonia of lobar dimensions, occupying the entire left lower lobe and the adjacent part of the right upper lobe. On section the consolidated tissue was greyish white, firm, and comparatively dry. There was no suppuration, and the bronchioles were moderately thickened. The tissue was tough as if a diffuse fibrosis or carnification was present. The lymph nodes were practically normal, and pleural reaction limited to small isolated patches of surface dulling. The right lung was congested.

Histologically there was a great karyorrhexis of polymorphonuclear and endothelial cells. Bronchioles were partially filled with an exudate containing broken down polymorphonuclear and endothelial cells. The alveolar cells were filled with red blood cells and fibrin, with a small number of these cells described. The pleural coat was not seen in the section examined. The liver showed a cloudy swelling and congestion. Another section of lung showed severe congestion and edema.

CASE 4.—D. A., a white boy, eight years old, was admitted to the Mount Sinai Hospital on Apr. 19, 1932.

It was impossible to obtain the family history or the past medical history.

According to the patient's brother, the child had been fairly well until the day before admission, when he became sick and complained of a pain in his chest.

The child was semiconscious, restless, and delirious, having had visual hallucinations. He was poorly nourished, with cyanotic lips and hands and cold and clammy skin and extremities. A rash was present over the chest and arms. The child was breathing very rapidly with apparent difficulty, but there was no movement of the alae nasi and no retraction of the epigastrium or intercostal spaces. The neck was not rigid. The pupils were equal and reacted to light, but the eyes were dull, and there was a scum over the right cornea. The pulse was barely perceptible. The cardiac boundaries were normal, and the heart sounds were weak. The whole right chest was dull on percussion, and the breath sounds, suppressed, somewhat harsh, and accompanied by some râles. The interne had noted impairment at the left base with rather harsh breath sounds but no râles. The abdomen was distended and tympanitic. Kernig's sign was absent. Both legs, however, seemed to be rather spastic, and there was marked tenderness in the knee joints.

The child was placed in an oxygen tent and given 30 grains of quinine and urea hydrochloride intramuscularly, 2 ampules of glucose intravenously, 1 c.c. of pituitrin, 1 dram of digalen, and 1/30 grain of strychnine sulphate subcutaneously and milk of asafetida by rectum.

The child became very restless, yelling, screaming, and fighting the oxygen tent, which in consequence was removed. Later the child became more quiet and tried to cough. The pulse became imperceptible; the dyspnea and cyanosis increased; and the boy died one hour after admission.

The autopsy and histologic examination were made by Dr. David R. Meranze, who made a diagnosis of diffuse myocarditis, early interstitial pneumonia of both lungs, congestion of the thymus, cloudy swelling, fatty degeneration and congestion of the liver, congestion and edema of the pancreas, cloudy swelling and congestion of both kidneys, and acute mesenteric lymphadenitis.

The left lung came away freely from the chest wall. The upper lobe was pinkish and on section showed a moderately congested, well-aerated, normal surface. The lower lobe was bulky and had a generally bluish cast. It contained less air than normally. On section it was purplish red in color, markedly congested, had a suggestion of granularity, and seemed somewhat more solid than normally. The bronchi of the lower lobe contained a small amount of a thin, slightly purulent exudate. The lymph nodes about the hilum were deep purple in color, and on section were markedly congested. The right lung showed the same involvement as that of the left lower lobe, possibly to a less marked degree. The middle lobe alone seemed to have escaped the process described.

On microscopic examination the lung was found intensely congested. The septums were greatly thickened by congestion and some degree of round cell infiltration. In some regions actual interstitial and even intraalveolar hemorrhage had occurred. Many alveoli were filled with edematous fluid, desquamated epithelium, and some inflammatory cells. The pleura was thickened by edema.

CASE 5.—C. C., a white infant girl, aged eight months, was admitted to the Mount Sinai Hospital on Dec. 12, 1931.

The baby had been delivered at term with instruments and probably had been asphyxiated. She had been bottle fed from birth and was apparently gaining in weight. She had received three transfusions at another hospital for weakness and anemia but had otherwise been well, never previously having turned blue or breathed rapidly.

One week before admission the baby suddenly developed a cough and high fever, which condition improved for a few days under treatment and then became worse. The spasm of coughing became so severe on the day preceding admission that the child turned blue. At times the cough produced vomiting.

The infant was markedly undernourished, looking like one three months old, rather than eight. She appeared acutely ill, with marked cyanosis, especially of the lips, some respiratory distress, and marked playing of the alae nasi. The temperature was 102° F.; the pulse, 160; and the respiration, 72. The tonsils and pharynx were injected. There was no nuchial rigidity.

The cardiac boundaries were normal. The heart action was very rapid and irregular. The first sound was fair at the apex but poor at the base.

Examination of the lungs disclosed dullness bilaterally above the fourth rib, anteriorly, posteriorly, and in both axillae, being more marked on the right posteriorly; also dullness on the right posteriorly below the sixth rib. Tactile fremitus was increased bilaterally over the upper lobes, to a less extent on the left. The breath sounds were somewhat harsh. Crepitant and subcrepitant râles were scattered throughout the chest. One examiner heard some fine crackles at the right base.

The abdomen was soft and not distended. The spleen was barely palpable. The liver was not enlarged. Kernig's and Brudzinski's signs were absent.

The hemoglobin was 65 per cent, the red blood cell count was 3,490,000; and the leucocytes, 29,400 with 60 per cent polymorphonuclears.

The child was placed in an oxygen tent and given liquids, glucose, sodium citrate, a mild mustard plaster around the chest, an enema of glycerin and asafetida, and drops in the nose of a 1:5,000 metaphen solution. Five grains of quinine and urea hydrochloride were injected intravenously. Four hours later the baby was given 2½ grains of quinine hydrobromide, 2 minims of digalen, 5 minims of brandy, and 5 grains of sodium citrate orally, but vomited them all. Five grains of quinine and urea hydrochloride were then injected intramuscularly. A Murphy drip of a 5 per cent glucose solution was started. Two hours later the temperature was 106.4° F.; the pulse, 200; and the respirations, 80. The child looked very ill and toxic, was quite cyanotic, developed upward and lateral nystagmus, and vomited a prune-juice material. An hour later the child went into convulsions and became exceedingly cyanotic, the heart sounds being very feeble, the respirations remaining 80. Two hours subsequently the temperature reached 107.8° F.; the cyanosis became very marked; and râles were very evident throughout the chest. Death occurred two hours later.

The autopsy and microscopic examination were made by Dr. David R. Meranze, who made a diagnosis of cloudy swelling of the myocardium, fibrinous pleurisy, interstitial pneumonia of both lungs, diffuse hyperplasia and congestion of the spleen, congestion, cloudy swelling, and moderate fatty degeneration of the liver, congestion and cloudy swelling of both kidneys, and acute mesenteric lymphadenitis.

The left lung was free of adhesions and was about normal in size. The lateral aspect of both lobes, except for the upper half of the upper lobe, was externally reddish blue in color, non-air-containing, and on section a mottled purplish color with a fleshy aspect and feel. There was a suggestion of degeneration in the exposed tissue. The remainder of the lung was pink and air-containing. The bronchi were normal. The bronchial glands were also normal in appearance.

The lateral fringe of the lowermost portion of the upper lobe of the right lung and the lateral upper half of the lower lobe were also purplish areas, somewhat depressed and rather firmer than on the left lung. Small pinkish islands of tissue were scattered in these regions. On section the tissue was rather dry. Small, ochre-colored nodules were present, which seemed somewhat degenerated and separable from the remaining fleshy, purplish, involved tissue. The remainder of the lung, including the middle lobe, was practically normal. The hilum nodes were not involved.

On microscopic examination the pulmonary involvement was found to vary in kind and degree. In one area the process seemed of the lobar pneumonic type. In

other areas the process was most marked about the bronchi. In still others the alveolar septums were thickened by congestion and inflammatory reaction. The exudate was rich in polymorphonuclear cells but poor in fibrin. Intense congestion was everywhere a feature. Areas of collapse were present. The bronchi contained a purulent exudate. A fibrinous reaction was present in the pleura.

Bacteriology.—Heart blood culture—*Staphylococcus albus.*

CASE 6.—J. M., a nine-month-old white boy, was admitted to the dermatologic service of the Jewish Hospital on Feb. 25, 1932, with eczema. His mother had had eczema in her infancy, and the patient himself at the age of three years developed a very itchy exfoliative rash on the face, which had appeared and disappeared several times. Two months before admission the rash also appeared on the back and lower extremities, behaving like the face lesion. The baby had had many colds, and for the three months preceding admission had had coryza and cough. The child suffered from frequency of urination, was irritable, slept all day, and was awake all night.

Examination disclosed a rachitic baby with generalized papular eczema, producing excoriation of the glans penis, and with coryza and pharyngitis. Temperature, pulse, and respiration were increased. The heart and abdomen findings were negative. There was slight dullness over the right chest posteriorly, but there were no other abnormal chest signs. Dermatagraphia was present. The urine was normal. Skin protein tests proved negative. The hemoglobin was 71 per cent; the red blood cells, 4,500,000; and the leucocytes, 6,500 with 42 per cent neutrophiles, 55 per cent lymphocytes, 1 per cent transitionals, and 2 per cent eosinophiles. The Wassermann test was negative. Blood calcium was 10 mg. X-ray examination showed both lung fields clear, with no evidence of consolidation.

The eczema improved at first but later became pustular. Cervical adenitis and anemia developed. In addition to moderate dullness on the right posteriorly and in the axilla, there developed a slight dullness on the left anteriorly and in the axilla. Eleven days after admission a right otitis media occurred, and a month later, double otitis media.

Five weeks after admission the child developed an acute upper respiratory infection with a fever of 104° F., increased pulse and respiratory rates, coryza, pharyngitis, and cough. Two days later he had a slight cough, grunting expiration, and movement of the alae nasi. The heart was enlarged slightly to the left, and the heart sounds were fair. There was a diffuse, red, maculopapular eruption over the back and around the neck. Dullness was present over the whole right chest posteriorly and slight dullness in the right axilla, with increased fremitus, but there were no other definitely abnormal chest signs. The hemoglobin content was 55 per cent; the red blood cell count was 3,500,000, with slight anisocytosis, slight achromia, and occasional poikilocytosis; the leucocytes, 22,100, with 67 per cent neutrophiles, 32 per cent lymphocytes, and 1 per cent large mononuclears.

Twenty-five grains of quinine dihydrobromide were given by mouth over a period of twenty-four hours, during which time the temperature dropped to 98.8° F. Twelve hours later the temperature rose to 103°; there was playing of the alae nasi and impairment was noted on the left chest posteriorly over the eighth or ninth rib. The right ear was found inflamed and a myringotomy was performed. An x-ray examination of the chest taken during the second temperature rise showed both lung fields absolutely clear throughout, with no pulmonary pathology seen.

After three doses of 2½ grains each of quinine dihydrobromide, the temperature twelve hours later dropped to 99° F., where it remained for thirty-six hours, and then rose abruptly to 104.° The left eardrum, found reddened and bulging, was incised on the following day. A roentgenogram taken at this time showed consolidation in

the right upper lobe. Impairment was still present over the entire right lung, being more marked in the upper lobe. Dullness also was noted over the left lung, at first over the lower lobe, and on the following day over the upper lobe, associated with harsh breath sounds or tubular breathing and with crepitant râles. On the next day the child had a distressing cough, grunting expiration, marked movement of the alae nasi, and an inspiratory retraction below the costal margin. On the right chest there was dullness anteriorly above the second rib, in the axilla above the fourth rib and posteriorly above the fifth rib, all associated with increased fremitus and vocal resonance. There was dullness also on the left posteriorly above the fifth rib. The breath sounds could not be distinguished on account of the noise from the mouth and nose, but on the following day they were noted as distant and tubular. No râles were heard.

Fourteen doses of 5 grains each and seven doses of 2½ grains each of quinine dihydrobromide were given over a period of three and a half days, during which time the temperature first dropped to 101.4° F. and thereafter fluctuated between 104.6° and 102.4°. The blood picture six hours after the last dose of quinine was the same as that taken previously, except that the neutrophiles were 81 per cent, and the lymphocytes, 19 per cent. The temperature remained elevated for a day and a half longer until the patient died. During the last five days the pulse fluctuated between 140 and 172, and the respirations, between 30 and 60.

Blood culture showed pneumococcus Type IV.

In addition to 117½ grains of quinine the baby received 2 minims of tincture of digitalis three times a day, nasal disinfection with a 1:5,000 solution of metaphen, inhalations of carbon dioxide and oxygen for ten minutes every two hours (the child later being placed in an oxygen tent), and, after the quinine was stopped, 5 minims of creosote carbonate every four hours.

The autopsy and histologic study were made by Dr. B. A. Gouley, who made the diagnosis interstitial pneumonitis of the upper lobe of the right lung and cloudy swelling of the other organs.

The findings of chief interest were in the lungs. The right lung showed a complete consolidation of the upper and middle lobes. The remaining lower lobe, as well as the left lung, was practically normal. The consolidation was white or pinkish and yellowish white and unusually firm and dry. The cut surface was very smooth. In some areas the consolidation appeared to be the result of confluence of smaller lesions. No pus was noted, and the bronchial tree was moderately congested. The appearance of the pulmonary lesion was definitely unlike that of the ordinary pneumonias. The mediastinal lymph nodes were of normal appearance.

On histologic examination numerous lung sections showed complete consolidation although the density of cellular infiltration varied in different fields. There was an irregular interstitial infiltration, very marked in some fields and minimal in others. It consisted of rather large round cells and also irregular epithelioid cells; these two types were usually associated with each other, sometimes forming large isolated nodules, usually perivascular, that tapered out interstitially or else broke into the alveolar spaces, filling and obliterating them. Occasionally multinucleated cells were seen in these nodules. Small groups of very irregular epithelioid cells were often clustered around small foci of fibrinous (fibrinoid) necrosis.

The alveoli were filled with fibrin; some contained no cells or very few, but in other fields there was a heavy alveolar infiltration. This alveolar exudate contained only a small percentage of polymorphonuclear cells, and in many alveoli apparently none were present. The cells were often very small or fragmented and of irregular shapes, suggesting a strong similarity to the interstitial infiltration. In some large areas this cellular invasion was so dense that the entire lung structure was ob-

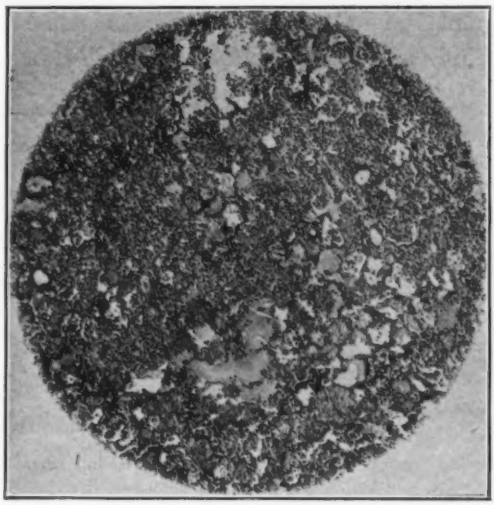

Fig. 1.—Acute interstitial pneumonia (×61). Case 6. Note the thickened alveolar walls and the "pouring over" of the exudate into the alveoli. In the upper left quadrant the infiltration is heavy. In other places the alveoli are filled with fibrin or serum.

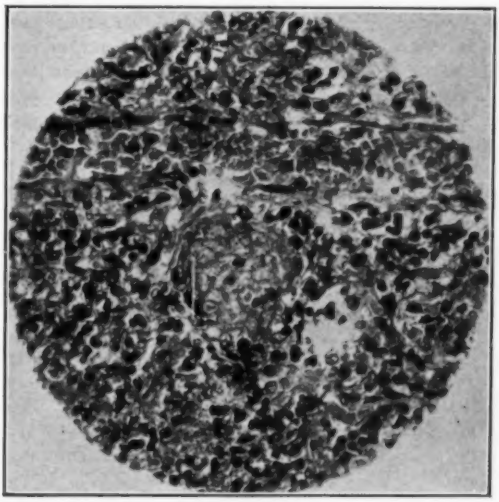

Fig. 2.—Acute interstitial pneumonia (×490). Case 6. Note interstitial (interalveolar) infiltration of round cells and "epithelioid" cells and the invasion of the alveolus (lower left) by the same type of cells.

scured. The fibrin here had a granular stippled appearance. In many fields, but especially in these densely cellular areas, the alveolar walls had been converted into strips of fibrin ("fibrinoid" degeneration).

This very cellular infiltration with its fibrinous degeneration of the alveolar walls was not an abscess formation; not only was this conclusion drawn from knowledge of the gross appearance, but from the absence or near absence of polymorphonuclear cells.

In a few fields there were noted small isolated groups of alveoli where the exudate consisted of fibrin, desquamated alveolar cells, and a small to moderate number of polymorphonuclears. The alveolar walls here were not infiltrated, and in these small areas the pathology was apparently entirely different from that noted above and was of the type normally associated with pneumococcus infection. The small bronchioles were filled with a very cellular exudate, identical with that seen in the largest portion of the section. The bronchiolar mucosa and wall were intact throughout and the exudate in the lumen was very likely an aspiration from the alveoli rather than a true bronchiolitis.

The larger blood vessels, particularly branches of the pulmonary artery, often showed small necrotic foci of epithelioid cells in the adventitia and media. One large vessel was recently thrombosed.

The interalveolar capillaries were markedly congested but where the fibrinous degeneration of the alveolar wall was more or less complete, they had disappeared.

The following two cases occurred on the service of Dr. Harry Lowenberg at the Mount Sinai Hospital and are reported with his permission.

CASE 7.—E. S., a six-month-old white girl, was admitted Dec. 7, 1931. The baby, born two weeks prematurely, probably had been asphyxiated and had had a collapsed lung. During the three days preceding admission the child had vomited, had high fever, had a slight cold and cough, and had suffered some loss of weight.

On admission the temperature was 104° F.; the pulse, 160; and the respiration rate, 48. The child looked acutely ill and was very flabby and below the normal weight. The respirations were not labored, nor was there playing of the alae nasi or cyanosis or cough. The nose, ears, and throat were practically negative. The heart was negative. The lungs exhibited no definite abnormal signs. The abdomen was practically normal.

X-ray examination on the day of admission showed an irregular consolidation of the lower portion of the right upper lobe, which on the following day showed some extension. Three days later x-ray plates disclosed in addition an incomplete consolidation of the left upper lobe.

The hemoglobin was 70 per cent, the red blood cells, 3,900,000; and the leucocytes, 20,400, with 65 per cent polymorphonuclears, 34 per cent small lymphocytes, and 1 per cent large lymphocytes.

On the day following admission the temperature dropped to normal; the condition seemed better; and the physical signs were all indefinite as to clinical pneumonia. Two days later the temperature went to 106.6° F., the pulse, to 200; and the respiration rate, to 80; but the chest was still negative, according to physical signs, and the ears, nose and throat were negative. The following day the child looked very much worse, and pathology could be demonstrated in both lungs, mostly in the right. The baby grew progressively worse; the temperature rose to 108° F. and the respiration rate to about 90, the pulse being too rapid to count. The baby became very cyanotic, but the heart sounds remained of fairly good quality, al-

though the first and second were alike. Râles were heard on both sides anteriorly and posteriorly. Pulmonary edema set in; cyanosis became more marked; the heart sounds became poor, there developed marked respiratory embarrassment; and death ensued.

Treatment consisted of the use of an oxygen tent, cooling bath, sodium citrate, glycerin-asafetida enemas, normal saline by hypodermoclysis, atropin, pituitrin, and the insertion of a rectal tube.

The autopsy and the microscopic examination were made by Dr. Meranze, who made the diagnosis of interstitial pneumonitis of both lungs, congestion, cloudy swelling and some fatty degeneration of the liver, congestion of the spleen, and marked congestion and moderate cloudy swelling of the kidneys.

The left lung was of normal size, with no adhesions. No pleurisy was present. The outer half of the upper and lower lobes, a somewhat pyramid-shaped area, the apex of which was the hilus, was semisolid and purplish in color. The overlying pleura was injected and irregularly blotched with minute ecchymoses. This region on section had a reddish purple aspect and was fleshy. Medial to it was a narrow fringe of depressed bluish tissue. The remainder of the lung was normal. The bronchi and hilum nodes were normal.

The entire lower lobe and the outer half of the middle lobe of the right lung were similarly involved in a fleshy non-air-containing, reddish purple process over which the pleura was injected. Here and there on section in the involved area was seen a small intensely reddish purple area, almost nodular in outline.

On microscopic examination the pleura was uninvolved. Very little of the lung studied was normal. Congestion was marked throughout. Large areas were involved in an inflammatory process which was predominantly interstitial and in which round cells and plasma cells were predominant. In some regions exudate into the alveoli was present, and there the exudate was often scanty in cells, containing some polymorphonuclears, and relatively dense in fibrin. In other areas the alveolar exudate was dense. Hemorrhage was a striking feature and was present interstitially and within many alveoli. Some of the smaller bronchi contained cellular exudate; the larger branches were clear. Many sections of lung showed collapse and compensatory emphysema.

CASE 8.—A. V., a white male baby, thirty-three months old, was admitted Dec. 9, 1931.

The birth was normal, but the delivery was instrumental, the labor being dry. The baby was breast fed for nine months and had had no feeding difficulties. He had had measles, an abscess under the chin, and frequent colds, but no sore throat.

He was well until the day before admission, when with no apparent cause he started to vomit—at first mucus, later greenish water. He was very feverish. At 1 A.M. on the day of admission he had a convulsion accompanied by loud screaming, lasting about five minutes. The temperature was high, and he was delirious all night, dozing for short periods and drinking fluids copiously. He had another convulsion at 4:30 P.M., after which he was admitted to the hospital.

On admission the temperature was 107° F.; pulse, 200; and respirations, 38. He was acutely ill, semicomatose, breathing rapidly, and showing an expiratory grunt. The head and ears were negative. The eyes were staring; the pupils were equal and reacted to light and accommodation. There was some left lateral nystagmus. The nose was normal; the pharynx, injected; and the tonsils, enlarged. There was no adenopathy or rigidity of the neck. The heart showed accentuation of the pulmonic second sound but no murmurs.

Over the right chest percussion was impaired, and there were some small rather indefinite râles.

The abdomen showed some distention, but no tenderness or rigidity.

The liver and spleen were not palpable. The knee jerks were exaggerated, especially on the right. There was a suggestion of Kernig's sign on the right.

Some three hours later, although the child was critically ill, semiconscious, stuporous and feverish, the respirations were not labored, and there was no playing of the alae nasi and no grunting. Heart and lungs were found negative. There was no nuchial rigidity, Babinski's sign, or ankle clonus. Brudzinski's contralateral sign was present, and at times Kernig's sign was positive. Later there was general trembling of the body when the child moved or turned, and the lower extremities in general were spastic. Spinal puncture revealed a clear fluid under moderately increased pressure. The leucocytes numbered 29,300, with 94 per cent polymorphonuclears, 4 per cent small mononuclears, and 2 per cent large mononuclears. The spinal fluid was negative. The blood sugar was 130. There was no growth on blood culture. The blood calcium was 10.2 mg. X-ray examination showed no evidences of pulmonary consolidation or pleural effusion.

The following day a few sticky râles were heard at the end of inspiration over the left lower base posteriorly. There was also some evidence of tetanic spasms. Later in the day impaired resonance was noted just above the left base posteriorly, with harsh breath sounds and occasional râles on inspiration.

X-ray pictures showed a suggestion of an early pneumonia in the left base behind the heart, which evidence was too incomplete for definite diagnosis.

During the night the child had a convulsion. On the next day the physical signs of consolidation of the left lower lobe were much more distinct.

Twelve hours later the patient was very ill, with temperature over 108° F., and was very cyanotic. He became rigid at times and at times assumed opisthotonos. The eyes were glazed and half closed. The chest was full of large gurgling râles. The heart sounds were of poor quality and embryocardiac and became weaker, though there was no pulmonary edema; the baby died. Spinal puncture was made an hour before death and 12 c.c. of clear fluid were obtained under slightly increased pressure.

The autopsy and microscopic studies were made by Dr. David R. Meranze, who made a diagnosis of congestion of the right lung, interstitial pneumonia of the right lung, congestion of the spleen, cloudy swelling of the liver with congestion and edema, and congestion and cloudy swelling of the kidneys.

The upper lobe of the left lung was normal. The pleura of the outer two-thirds of the lower lobe was dulled and thinly covered by a readily removable greenish layer of fibrinous exudate. The underlying lung tissue was firm and non-air-containing. The extreme lowest fringe was especially firm. The involved lung area on section had a swollen purple fleshly aspect and in which area there was much blood. The harder lowest fringe just mentioned was pinkish and entirely dry and rubbery in consistency. The bronchi and hilum nodes were normal.

The right lung weighed 180 gm. It was large, pink and air-containing. Its bronchi and glands were normal.

On microscopic examination the tissue of the right lung was merely congested as was also some of the uninvolved portions of the left. The involved portions showed predominantly a hemorrhagic type of interstitial pneumonia in which the cellular exudate contained few polymorphonuclears. In some regions the exudate was alveolar, but here, too, the interstitial tissue was involved. Marked congestion and areas of collapse were present. Some of the veins contained purulent material. The pleura was the seat of an acute fibrinous pleuritis.

Two cases of pneumonia that I treated at the Mount Sinai Hospital, in which recovery took place, I believe to be instances of acute interstitial pneumonia, but as this is impossible to prove, they have been omitted. One was in a fourteen-month-old girl, who was given a total of 70 grains of quinine, and the other, in a boy, one year old, who received in all 57½ grains of the drug.

ANALYSIS OF THE CASES REPORTED

The most characteristic common feature in the eight cases reported is the histologic appearance of the areas of interstitial pneumonia. Most of the cases showed a capillary engorgement and an infiltration of round cells and epithelioid or plasma or endothelial cells and in some instances polymorphonuclear cells, which was not abscess formation (Figs. 1 and 2).

The feel of the affected portion of the lung is also characteristic, being more like that of muscle than lung tissue. This does not always appear from the descriptions, which employ the terms "firm," "fleshy," "rubbery," "bulky," "of increased consistency," "semisolid," "more solid than normal," and "tough, like a diffuse fibrosis or carnification."

The color of the affected portion of the lung was peculiar, being variously described as blue, purple, pinkish, greyish red, ochre, greyish yellow, greyish white, and white.

A noteworthy circumstance was absence of suppuration.

There was nothing characteristic about the location of the lesions, which was given in seven of the cases. The right upper lobe was involved in five cases; the right middle lobe, in two; the right lower lobe, in four; the left upper lobe, in three; and the left lower lobe, in five.

Pleural involvement was rare, absence of excess fluid in the pleural cavity being marked in five cases. Fibrinous exudate was observed in only one case although there was dulling in another case and studding with minute ecchymoses in two cases.

Culture of the heart blood was made at autopsy in one case with growth of *Staphylococcus albus.*

The clinical course of the disease, the symptomatology, the physical findings, the roentgenologic examination, and the laboratory tests, as observed in the cases reported, present nothing that can be regarded as characteristic of this peculiar form of acute interstitial pneumonia or as distinguishing it from other forms of pneumonia. This may be due in part to the paucity of cases and to the brief stay in the hospital of most of the patients, half of whom died within twelve hours after admission.

The most prominent clinical features are the short duration of the disease in most of the cases, the virulence of the infection, its fatality, and its failure to respond to treatment. The ages of six of the patients

were between four and nine months. One child was thirty-three months old, and one was eight years old.

The duration of the disease in the eight cases was two, four, seven, eight, eight, nine, ten, and eleven days, respectively. The onset was sudden in five of the cases. The acute interstitial pneumonia was preceded by an attack of coryza in two cases.

The initial symptoms were cough in five cases, coryza in four, fever in four, grunting respiration in two, vomiting in two, and pain in the chest, fretfulness, delirium, laryngeal stridor, convulsions, and movement of the alae nasi in one case each.

Symptoms exhibited after admission to the hospital were cyanosis in six cases, cough in five, dyspnea in five, a grunting respiration in four, coryza in four, movement of the alae nasi in three; semiconsciousness, inspiratory retraction of the chest, convulsions, skin eruption, and nystagmus in two each, and pain in the chest, delirium, vomiting, and laryngeal stridor in one case each.

The highest temperature in each case was 108°, 107°, 106.8°, 105.8°, 104.6°, 104.2°, 104°, and 103° F., respectively.

The highest pulse rate in each case was 200, 200, 200, 172, 148, and 124, respectively, while in two cases the pulse was imperceptible.

The highest respiratory rate in each case was 88, 86, 82, 80, 60, 60, 54, and 48, respectively.

Dullness on percussion was noted in every case, increased fremitus in two cases, increased vocal resonance in one case, suppressed breath sounds in one case, harsh or rough breath sounds in six cases, and râles in six cases.

Distention of the abdomen occurred in four cases.

The hemoglobin varied from 40 per cent to 70 per cent; the red blood cells, from 3,150,000 to 3,900,000; the leucocytes, from 6,500 to 29,400; and the polymorphonuclears from 55 per cent to 94 per cent. Blood cultures during life are recorded in only two cases—Pneumococcus Type IV growing up in one, while the other showed no growth.

Resistance to treatment was characteristic of these eight fatal cases. Of special significance to me was the resistance to quinine therapy, which is in marked contrast to my experience with the use of quinine in cases of ordinary lobar and bronchopneumonia in both children and adults[1] in whom quinine has seemed to have a decided effect in combating the toxemia, favorably affecting the general symptoms, and shortening the course of the disease.

CRITICAL REVIEW OF THE LITERATURE ON INTERSTITIAL PNEUMONIA

Considerable confusion exists in medical literature on the subject of interstitial pneumonia. This term has been applied to a number of different conditions which have not always been clearly differentiated.

Some authors, while discussing one type, quote cases reported by a writer who is describing a different type, apparently without recognizing this fact. Moreover many different names have been employed to indicate the same process and the same designation has been used for different processes. In searching for references to the peculiar form of acute interstitial pneumonia here reported it therefore became necessary to study carefully in the published articles the macroscopic and histologic descriptions of the lungs regarded as being affected with interstitial pneumonia.

Chronic interstitial pneumonia is the form most frequently mentioned in the textbooks. It was described first by Corrigan, who called it cirrhosis of the lung.[2] It since has accumulated a variety of characterizations: interstitial pneumonia, chronic interstitial pneumonia, interstitial chronic lung inflammation, productive interstitial lung inflammation, pleurogenic interstitial pneumonia, productive fibrous pneumonia, chronic fibrous pneumonia, fibroplastic pneumonia, productive fibroplastic pneumonia, productive pneumonia, chronic pneumonia, indurative pneumonia, chronic indurative pneumonia, infiltration of the lung with induration-matter, collapse-induration, pneumonoconiosis, pulmonary sclerosis, pneumonia fibrosa chronica, carnification, inflammatory carnification, contracted lung, fibroid phthisis, pneumonia with organization of the exudate, ulcerative pneumonia, parenchymatous pneumonia, lymphangitis reticularis, lymphangitis trabecularis, lymphangitis nodosa, and fibrous perivasculitis. This includes the types described by Walshe,[3] Delafield,[4] Heitler,[5] Jacobi,[6, 7] Feer,[8] von Jürgensen,[9] and von Honsemann.[10] In 1884 Heitler made the statement that all German authors previously had regarded interstitial pneumonia as chronic.

A subacute interstitial pneumonia also has been noted by Heitler,[5] Jacobi,[7] and others, the first including it under his primary parenchymatous pneumonia. Finkler[11] quotes Hanau as calling it progressive, intraalveolar, indurated pneumonia and Orth as naming it pneumonia with organization of the exudate. Jacobi[7] prefers the term "pulmonary hyperplasia with secondary cirrhosis." This form is regarded by Wagner,[12] Eppinger (quoted by Heitler[5]), and Hanau (quoted by Finkler[11]) as a primary independent disease of the lung parenchyma, which develops independent of other affections of the lungs and independent of any affection in the organism whatsoever. On the other hand, Marfan,[13] Finkler,[11] Eichhorst,[14, 15] Gluzinski (quoted by Finkler), Hershe and Woronichin (quoted by Heitler), and Marchand (quoted by both Heitler and Finkler) believe it is an outcome of a croupous pneumonia, a view which Henoch[16] questions.

Acute interstitial pneumonia is rarely referred to in textbooks on pathology, pediatrics, and medicine but is discussed more frequently in monographs and medical journals. Several distinct forms have been

described although the same distinctions are not recognized by all the different observers.

Acute interstitial bronchopneumonia following measles, pertussis, diphtheria, and other infectious diseases with respiratory involvement has been noted by Bartels,[17] Kromayer,[18] Marfan,[13] Honl,[19] Koester,[20] Steinhaus,[21] Hart,[22] Jochman and Maltrecht,[23] Feer,[8] MacCallum,[24] Opie, Blake, Small and Rivers,[25] Holt and McIntosh[26] and Hecht,[27] the last-named calling it giant-cell pneumonia, a classification regarded by Karsner and Meyers[28] and Moore and Gross[29] as not justified. Preferable designations are the terms "focal pneumonia with peribronchial extension," according to Lauche[30] and "bronchogenous focal pneumonia," and "bronchopneumonia with peribronchial extension," according to Kaufmann.[31, 32]

An acute interstitial pneumonia following, or occurring in, influenza, especially during severe epidemics, is looked upon by some writers as identical with the type just mentioned and by others as a different form. Hosack,[33] Hudson,[34] M'Reynolds,[35] Stearns,[36] and Mann[37] described cases they observed among soldiers and civilians during the War of 1812 and MacCallum,[24] Wolbach,[38] and Opie, Blake, Small, and Rivers[25] studied cases occurring in the army camps during the World War. This form of pneumonia has been variously termed pneumonia notha, peripneumonia notha, pneumonia typhoides, peripneumonia typhoides, typhoid pneumonia, primary streptococcus pneumonia, erysipelatous pneumonia, erysipelas of the lung, bilious pneumonia, putrid pneumonia, and malignant pleurisy. Kuczynski and Wolff[39] include lymphangitic or interstitial pneumonia among the grippal forms of pneumonia, while the term "focal pneumonia with peribronchial extension" is applied by Lauche[30] to this form as well as to the one previously discussed.

Lymphangitic pneumonia is the only true form of interstitial pneumonia, according to von Honsemann,[10] Lauche,[30] and Kaufmann.[31, 32] Several types of this form were tabulated under "chronic interstitial pneumonia." A number of different designations occur also in the acute types, including interstitial lymphangitic pneumonia, pleurogenous pneumonia, lymphangitis exudativa, lymphangitis proliferans, acute lymphangitis, peribronchial lymphangitis, peripneumonia, suppurative pneumonia, suppurative peripneumonia, perilymphangitis, perivasculitis, suppurative interstitial lung-inflammation, suppurative fibrinous pneumonia, suppurative peribronchial lymphangitis, pleurogenous interstitial pneumonia, peribronchial pneumonia, serofibrinous interstitial lung inflammation, and pneumonia desiccans. This is the form of interstitial pneumonia in the cases described by Smith and Langmann.[51, 52]

None of the descriptions of the various forms of interstitial pneumonia enumerated above fits the cases here reported, although in one of two types of influenzal pneumonia observed by Wolbach[38] at Camp

Devens, Mass., the lung tissue in patients dying within a few days after the onset of pulmonary signs was dark red and "meaty in consistency."

The peculiar form of acute interstitial pneumonia exhibited by the cases here reported, therefore, would seem to be extremely rare. The only references to conditions closely resembling it that I have been able to find are in articles by Corrigan,[40-44] Stokes,[45] Gordon,[46] Leichtenstern,[47, 48] and Buhl (quoted by Leichtenstern[47, 48]), in the fifth and subsequent editions of George B. Wood's *Practice of Medicine*,[49] in which Gordon is quoted and in a recent report on rheumatic pneumonia by Gouley and Eiman.[50] These conditions have been termed blue pneumonia, acute induration of the lung, asthenic pneumonia, acute lobular cellular pneumonia, acute lobar desquamative pneumonia, inflammatory carnification, and rheumatic pneumonia.

Leichtenstern[47, 48] describes a rare but important clinical form of cellular pneumonia occurring in influenza and other infectious diseases, such as scarlet fever, whooping cough, and measles which he calls acute lobular cellular pneumonia and which he states has absolutely nothing to do with the so-called primary streptococcus pneumonia. "It often arises acutely," he says, "like a croupous pneumonia and attacks immediately a whole lobe, generally the upper lobe. Clinically it gives the impression of a croupous lobar pneumonia until postmortem examination discloses its true character. The cut surfaces of the lung are entirely smooth, homogeneous, of a fleshy red to a bluish red color, of a fleshy, elastic consistence, and totally devoid of air. Neither fluid nor air can be expressed; nor do drops of pus flow from the severed bronchi. It is a great error to assume that these acutely arising lobar infections are formed by the confluence of lobular areas or result from an ordinary bronchopneumonia. They belong neither clinically nor pathologically to the latter. Histologically, the pneumonia is characterized by extreme vascularity. The alveolar septums are broad and the seat of round cell infiltration; the lumina of the alveoli are filled with cells, but only traces of fibrin can be detected. The cells consist of a small number of red blood cells, the larger number of leucocytes, but notably large epithelioid cells, which we believe to represent desquamated alveolar epithelium. This peculiarity differentiates it, from a purely histologic point of view, from the usual catarrhal pneumonia, which, on account of the large number of leucocytes, represents pus formation in 'optima forma,' as Pfeiffer terms it. The acute lobar desquamative pneumonia described by Buhl, which has unjustly been forgotten, is clinically and pathologically almost identical with the form which we are now considering, namely the acute lobular cellular pneumonia. On account of the fleshlike consistence of the infiltrated lobe, we have in the past used the expression 'inflammatory carnification.' We must, however, now withdraw this name, as Weichselbaum and Kundrat have lately used it

to designate something quite different, namely, chronic indurative process. Rusty sputum is never seen. The appearance of this sputum alone makes the differential diagnosis from croupous pneumonia possible; no other sign is absolutely pathognomonic."

In 1841 both Corrigan[40, 41] and Stokes[45] exhibited before the Pathological Society of Dublin specimens of a rare form of pneumonia then prevalent, presenting a number of remarkable characteristics. Other cases were reported by Corrigan[42, 43, 44] and by Gordon[46] during a similar epidemic some years later. Stokes regarded the disease as an acute induration of the lung differing from ordinary pneumonia. Corrigan called it blue pneumonia at first and later asthenic pneumonia.

The following is the description of these observers:

The color of the lung when first seen after opening the thorax was a deep blue, bordering on purple, like a dark blue plum. This appearance, however, was very evanescent, fading away rapidly and being almost completely lost in the course of three or four hours, the lung then becoming grey or iron grey in color.

The lung was firm and solid, and exceedingly heavy and tough, but had none of the characteristics of acute hepatization from pneumonia and did not pass into the state of red or grey hepatization, the disease having no tendency to terminate in hepatization or suppuration. At times the lung was friable or brittle, at other times requiring the greatest force to break it down. The lung did not crepitate under the finger, thus differing from the first stage of ordinary pneumonia. When grasped in the hand, the lung felt like muscle, resembling carnified lung, but differing from it in retaining its original bulk. It sank in water. It did not pit on pressure, nor did it appear as much swelled as is usual in ordinary cases of pneumonia.

When cut, the lung did not exude any quantity of blood. The cut surface did not exhibit the granular surface of ordinary pneumonia. Where a section of the lung was made the color was iron grey, somewhat like that of the lung in the vicinity of gangrenous spots.

In this early stage the disease seemed to be a simple congestion of the capillary vessels. There was no effusion of lymph, no tendency to pass into the second stage, no trace of purulent matter anywhere. The congestion was of a peculiar kind; there was no exudate of serous or bloody fluid. It was accompanied with that state of vessels characterized as the state of passive congestion. Corrigan believed it to be a state of the lung in which the vessels are too weak and too much distended to be capable of contracting and regarded this atonic state of the vessels as one of the characteristics of the disease.

The disease proved fatal either directly in the first stage of congestion—in which it was, indeed, a very fatal disease, the patient dying when the lung was gorged and dark—or it passed from the first into the third stage, scarcely showing at all the second or hepatized stage. According to Gordon, the lung seemed readily to pass into a condition somewhat allied to gangrenous degeneration with effusion into the bronchial tubes, the patient dying of asphyxia. The lung then was of a dirty grey color; there was no well-marked suppuration, but a species of general softening, and commencing decomposition.

The clinical descriptions by Corrigan and Gordon cannot be said to give a characteristic picture of the disease, enabling one to distinguish

it from other forms of pneumonia. In several aspects, however, they bear some resemblance to the cases reported here.

According to these descriptions, the peculiar features of the disease were its assuming a bad and intractable character, its resistance to treatment, and its very rapid progress (some patients dying within a few hours from the onset of the attack), and the fact that the disease seldom extended over a period of weeks. Another feature, according to Corrigan, was shortness of breath, which is described by the patient as his most prominent symptom. The respiration may remain at 60, and sometimes is chiefly abdominal. The most remarkable feature in some of the cases was the great depression of strength; in no disease, Corrigan said, could the asthenic character be better marked. Indeed asthenic pneumonia was the name this author[6] gave to this type, and George B. Wood[49] placed under asthenic or typhoid pneumonia the reference to Gordon's article which he inserted in the fifth edition of his *Practice of Medicine*. A child under Stokes's care died of exhaustion. Among the symptoms of those dying in the early stage Gordon lists excessive weakness, great depression of strength, great and sudden collapse, sudden lividity, and coldness of the skin, the face becoming purple and a dark flush arising on the face.

Some of the characteristic findings in the Dublin cases were not observed in the cases here reported. In the former the disease occurred at all ages and was found most frequently in the upper lobes.

A distinguishing symptom, according to Gordon, was the cough, which was altogether different in character from that of ordinary pneumonia, being very short, frequent, and performed without any apparent muscular effort whatsoever—very unlike the painful and distressing cough so often witnessed in vesicular pneumonia; however, a boy under Corrigan's care who had a cough said he was afraid to cough, owing to the pain it caused in his side.

Another distinguishing feature, according to Gordon, was that seldom was there much pain in the side, never the acute stabbing pain from the implicated pleura experienced in vesicular pneumonia, because pleurisy was rare.

In 1841 Stokes and Corrigan both stated that there were no symptoms of pleuritis, but in 1857 the latter said, "Pain is variable and appears to depend altogether on the degree of inflammation of the pleura; most generally, however, it is not much complained."

High fever, which attends vesicular pneumonia, was absent, according to Gordon. Corrigan says that the patient in this treacherous disease often does not seek admission into a hospital nor advice in private practice until too late, being deceived by the absence of pain, fever, and expectoration and feeling merely debility and shortness of breathing.

The pulse seldom was remarkably frequent, according to Gordon. It was always feeble and soon acquired a peculiar jerking feel. Yet in

those who died in the early stage, he described the pulse as small, feeble, and very rapid. The skin was of its natural temperature, or cooler than natural, and the face was rather sallow or yellow.

Both Corrigan and Stokes in 1841 noted as a peculiar and marked feature of the disease that it was not amenable to any of the usual modes of treatment. Since 1856, however, Corrigan and Gordon treated it with quinine in large doses with satisfactory results, the former recommending strongly its main treatment by quinine. Gordon believed that quinine evidently exercised a specific power over the disease. After thus treating for eight months all the cases of this form of pneumonia which he had witnessed, and having had the opportunity also of observing several cases similarly treated by Corrigan, he stated that the result of this treatment has been that, of the cases which came under observation before effusion had taken place into the bronchial tubes, none proved fatal, while some few recovered, even after the lips had become blue, the face congested, and mucous râles were audible in the bronchial tubes. This experience is quite at variance with mine, although I gave much larger doses of quinine than did Corrigan and Gordon.

In the cases of rheumatic pneumonia examined by Gouley and Eiman,[50] the gross and histologic pathology revealed pulmonary changes which apparently had not been previously described but which in certain particulars bear some resemblance to those seen in the cases here reported. The lesion is described as an acute interstitial inflammation, with no considerable exudate of polymorphonuclear cells. The color of the affected portion of the lung in six of the nine cases studied was deep blue, dark blue, slate blue, bluish, and dark red blue, respectively. The majority of the specimens showed but few lesions of their pleural surfaces.

SUMMARY

A rare and peculiar form of acute interstitial pneumonia was discovered at autopsy in six infants and two children. The most characteristic feature is the histologic appearance of the affected portions of the lung which present capillary engorgement and infiltration of round cells, epithelioid or plasma or endothelial cells, and in some cases polymorphonuclear cells, which is not abscess formation. Other characteristic features are the musclelike feel of the affected portion of the lung and its peculiar color. The cases studied presented no characteristic clinical, roentgenologic, or laboratory findings by which they could be recognized during life. The most prominent clinical features are the commonly short duration of the disease, the virulence of the infection, its fatality, and its failure to respond to treatment.

Of all the writers on interstitial pneumonia Leichtenstern, Buhl, Stokes, Corrigan, Gordon, and Gouley and Eiman are the only ones found by the author to describe conditions closely resembling this peculiar form of acute interstitial pneumonia.

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TRACHEOBRONCHIAL OBSTRUCTION PRODUCED BY TUBERCULOUS LYMPHADENITIS

Report of a Case in a Two-Month-Old Infant

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ALTHOUGH miliary tuberculosis is not uncommon in infants, the type of pathology observed in the following case together with the unusual clinical symptoms encountered present a picture deemed worthy of report.

CASE REPORT

F. H., white male, aged two months, was born in Multnomah County Hospital, March 11, 1934. The father and mother were in good health. There were four other children, aged seven, six, two, and one years. These were all well. There was no history of tuberculosis in the family and no known tuberculous contact. The mother's Wassermann test was negative. Labor and delivery were perfectly normal. Birth weight was 3,100 gm. Subsequent examinations and course in the nursery were normal. The baby was brought in to the out-patient clinic for regular monthly examination on April 12. He was nursing well and weighed 4,420 gm. Physical examination was entirely negative at this time. He was started on orange juice and cod liver oil.

On May 13, 1934, the baby was admitted to Doernbecher Memorial Hospital for Children with the history of having had a cold for about a week. He coughed considerably and was given nose drops. The previous day he began to have labored respirations. The baby was unable to nurse the following morning and consequently was brought to the hospital.

Examination.—The baby was well developed and nourished. He was having rapid, noisy respirations with an expiratory grunt. The color was good; he was alert and did not appear critically ill. Rectal temperature was 98.6° F. There was no evidence of inflammation or foreign body about the upper respiratory passages. There was marked sternal retraction with each respiration. Chest percussion revealed slight impairment over both apices. Breath sounds were roughened with an expiratory wheeze over the left chest and diffuse râles throughout both sides of the chest. The abdomen was not distended, and there were no masses palpable. The spleen was not palpable below the costal margin. Extremities were normal; reflexes, active.

Urinalysis was negative. Blood examination revealed hemoglobin, 55 per cent (7.6 gm.); erythrocytes, 2,360,000 per c.mm.; leucocytes, 11,500 per c.mm.; with the following differential count: polymorphonuclear leucocytes, 49 per cent; eosinophiles, 1 per cent; small lymphocytes, 24 per cent; monocytes, 11 per cent; staff cells, 15 per cent. Mantoux test (0.1 mg.) was negative.

Radiographs of the chest on May 15 and May 20 failed to reveal any evidence of opaque foreign body. There was a widening of the mediastinal shadow, suggesting enlargement of the thymus gland. The left diaphragm was markedly elevated;

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heart, pulled well over to the left side; right hilum, congested; there was some infiltration in the right upper lobe (these findings were reported as strongly suggesting a pneumonia in the right upper lobe area).

Course.—Shortly after admission the respirations became much more labored and the baby became quite cyanotic. He was placed in an oxygen tent and given subcutaneous fluids because gavage attempts seemed to increase the cyanosis. Temperature ranged from 98.2° to 101.2° F., staying fairly close to normal most of the time. Lung findings remained about the same, with bronchial breath sounds heard over the right apex and marked impairment to breath sounds over the left apex. Râles persisted throughout. The color improved somewhat while he was in the oxygen tent. But since the baby became quite restless and seemed to do as well out of the tent, the tent was discontinued for this reason on May 18. The use of a steam tent, atropine sulphate, and ephedrine and amytal was started. The baby showed a decided improvement until May 21, when he seemed to fight more vigorously

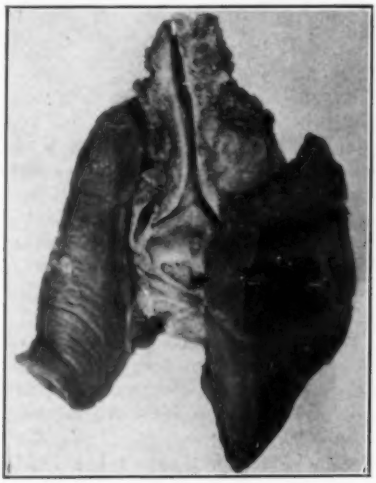

Fig. 1.—Photograph of gross specimen, showing group of caseous tuberculous lymph nodes deviating the trachea to the left and constricting the lumen of the left main bronchus. Miliary tubercles may be seen through the pleura of the left lung.

for breath. Practically no breath sounds were coming through the left chest. The heart rate became gradually slower in spite of stimulants, and the baby died on May 22, nine days following admission to the hospital. Symptoms appeared to remain of an obstructive nature throughout. There was no evidence of meningeal or cerebral involvement at any time.

Necropsy Report.—Necropsy was performed by Dr. Warren C. Hunter. Only the pertinent findings are recorded.

There were no pleural adhesions or exudate. The anterior margins of the lungs were blunt and emphysematous, and in the middle lobe of the right lung was an area of bullous emphysema measuring 2.0 cm. by 0.7 cm. Near the base of the lower lobe anteriorly was an area 2.5 cm. in diameter, where the pleura was raised up by closely set and confluent grayish yellow tubercles. These were directly continuous with other tubercles deeper in the lung substance. Over the posterior aspect of the lower lobe, beginning at the interlobar fissure and extending inferiorly, was a solid yellowish, slightly raised area, which extended down into the parenchyma

for a distance of 1.5 cm. Grossly, this had the appearance of caseous pneumonia. In addition, there were quite a number of typical solitary miliary tubercles under the pleura on the posterior aspects of both lungs. There were no further visible tubercules in the left lung. The parenchyma of each lung, where not tuberculous, was exceedingly bloody and exuded a frothy fluid on pressure. The trachea was deviated quite perceptably to the left, the larynx being 1.2 cm. to the left of a line drawn through the carina. The displacement was accounted for by the presence of a firm mass situated along the right border of the trachea, beginning at the bifurcation and extending upward for a distance of 2.3 cm. The mass was firm on palpation, and when sectioned, proved to be made up of a number of large lymph nodes which had become fused into one mass and were at the time somewhat indistinct. All had yellowish, caseous centers. This group of nodes lay posterior to the thymus and was entirely separate from it. In addition to compressing and deviating the trachea, the tuberculous mediastinal nodes had pressed upon the right common carotid artery and made its lumen oval shaped. The thymus was not above average size for a child of this age. At the bifurcation of the trachea was another mass 2.0 cm. in diameter. This had a fibrous capsule and a yellowish, caseous center. It had produced quite marked flattening and narrowing of the left main bronchus but had not affected the right.

With the exception of the right atrium, the cardiac chambers were contracted. There was no evidence of tuberculous pericarditis.

On the inferior surface of the liver and under the capsule of the spleen were a number of translucent miliary tubercles, and in the parenchyma of the latter were some caseous lesions.

Microscopic Findings.—Sections of the mediastinal lymph glands and right lung showed extensive tuberculosis. In these locations, the inflammatory response was partly proliferative and partly exudative. Elsewhere, namely in the left lung, spleen, and liver, the tubercles were of typical proliferative form, often with beginning caseation. The location of the lesions in the spleen and liver showed plainly their hematogenous origin.

Pathologic Diagnosis.—1. Focal caseous tuberculous pneumonia of the right lung.

2. Caseous tuberculous mediastinal and tracheobronchial lymphadenitis with tracheal and bronchial compression and deviation of the trachea to the left.

3. Hematogenous miliary tuberculosis of the liver and spleen.

SUMMARY AND COMMENT

The case history and necropsy report on a two-month-old infant are presented. The clinical course of an illness indicated tracheobronchial obstruction. The fact that there was no known source of tuberculous contact leaves room for speculation. During the clinical course there were no findings which definitely suggested a tuberculous origin of the disorder. Necropsy findings explained the obstructive symptoms. From the extent of the lesions, it appears unusual to us that there were no more clinical manifestations of tuberculosis. The anemia may have been due to the rapidly progressing tuberculous process. The pathologic lesions were more advanced than one would expect in a two-month-old infant.

THE TUBERCULIN PATCH TEST

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THE tuberculin patch test, carried out by applying to the unbroken skin a drop of undiluted old tuberculin, covering this drop with a patch of adhesive tape, and allowing it to remain in contact with the skin for forty-eight hours or longer, has been reported as a useful variation of the usual intradermal injection. Grozin[1] found an almost complete agreement in readings of the two tests. Wolff,[2] using tuberculin ointment, found 95.8 per cent agreement of tests performed with this material and Mantoux tests in which 0.1 mg. of old tuberculin was used.

Grozin pointed out that use of the contact test avoids the troublesome features of the preparation and administration of fresh tuberculin dilutions and eliminates the possibility of general systemic reaction and local necrosis. The last consideration is particularly applicable to negro children, in whom troublesome local reactions are rather common in our experience.

A group of patients were tested simultaneously with undiluted old tuberculin* by contact and 0.1 mg. of old tuberculin by intradermal injection. The results indicate that in cases in which the Mantoux is definitely positive, the contact test runs nearly parallel. The disagreement appears in those cases in which the Mantoux has been only slightly positive (one plus). Granting the difficulty of an accurate Mantoux reading in such cases, especially in the negroes, one must still attach sufficient importance to these slight intradermal reactions to lean toward the superiority of the intradermal method for general use.

Table I gives the groups on which the tests were made:

TABLE I

	TESTS AGREED			TESTS DISAGREED			PERCENTAGE OF AGREEMENT
	WHITE	COLORED	TOTAL	WHITE	COLORED	TOTAL	
1. Children under 2 years old	9	29	38	0	0	0	100.0
2. Children 2 to 14 years old	9	87	96	0	20	20	82.8
3. Adults	14	7	21	4	3	7	75.0
			155			27	85.2

From the clinics of the Charleston County Tuberculosis Association.

*The tuberculin used was obtained from George C. Hulpritt, Saranac. The skin was cleansed with acetone, which was allowed to evaporate thoroughly, and the tuberculin was placed on the skin with a glass rod. The drop was then covered with a square of adhesive tape of good quality (Drybak) and left in place for forty-eight hours.

Among these groups there were 107 positive and 75 negative intradermal tests.

There were twenty-seven instances in which the tests failed to agree, but in twenty-three of these instances the Mantoux reactions were only one plus; in two instances, two plus; and in only two instances were they four plus. In no case was the contact test positive when the Mantoux was negative. The Mantoux readings were made more on the basis of induration of the skin than on redness, for in some of the darker skins the difficulty of recognizing erythema was considerable.

Nine negro school children with positive Mantoux reactions and negative patch tests were given second patch tests, of which six were definitely positive and three negative. The reason for this change in response was not clear, unless the children had tampered with the adhesive tape in the original tests. Because the tape was removed by the children or otherwise loosened, it was necessary to discard a number of readings. The likelihood of such an occurrence is a real objection to the use of patch testing for groups of school children or other persons likely to remove the tape.

CONCLUSION

The tuberculin patch test seems to run in rather close agreement with strongly positive intradermal tests but is not comparable with the milder intradermal reactions. While the test presents some advantages over the Mantoux test, certain practical difficulties would seem to discourage its general substitution for the intradermal method.

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EXOPHTHALMIC GOITER BEFORE ONE YEAR OF AGE

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EXOPHTHALMIC goiter in preadolescence is uncommon; in childhood before five years, very unusual; and before one year, a real medical rarity.

White[1] in 1912 reported exophthalmic goiter in a newborn infant; Klaus[2] in 1914, in a nine-month infant; Helmholz[3] in 1926, in a child of eleven months. These three, plus one to be presented here, give a total of only four such cases predating one year of age which we have been able to find in the literature. The three first mentioned above are included in McGraw's[4] total of 157 preadolescent cases collected in 1928.

Because of its rarity the diagnosis of exophthalmic goiter in early childhood is quite frequently missed, and, even if diagnosed, the most effective line of therapy is much less well established than with the usual adult case. So to further, if possible, the total of medical and surgical experience in this condition, the following case is reported.

On Feb. 7, 1933, a little girl, aged two and one-half years, was brought by her mother to the Endocrine Clinic of the Children's Hospital of the East Bay, Oakland, Calif., with the complaints of nervousness, loss of weight, palpitation, and prominence of eyes.

She had been a seven-month, premature infant, weighing 4½ pounds, delivered normally. She was born in Utah, but the family had left there two months later and had lived in Oakland since. She was breast fed until she was three months old. At six months her eyes were definitely more prominent than normal. By nine months she was noticed to be unusually irritable, and attacks of vomiting and diarrhea began to recur. At one year of age she had a convulsion, and the examining doctor told the parents the child had a "bad" heart, its rate being far too rapid. Any excitement produced marked palpitation. About this time, too, the parents first noticed the swelling in her neck but did not consult any physician regarding it.

While she had been slender since the age of one year, her weight gains had been very good till the previous six or nine months, when she had actually lost 4 or 5 pounds. Her appetite had always been poor, especially for vegetables and meats, though she consumed generally about one and one-half quarts of milk daily. Her bowels had always been very irregular with alternating constipation and diarrhea, the latter generally associated with some vomiting. She had had three convulsive seizures during the past eight months. These lasted from two to three minutes and consisted of unconsciousness, twitching, and cyanosis without incontinence.

During the six months prior to her first visit to the clinic, the child had been much more irritable and nervous. Her eyes had become increasingly prominent during the last three weeks, and some tremor of her hands had been noted the last week or so. Her sleep had become quite fitful.

Her hair had always been scanty and fine. She perspired freely and easily. She passed through measles and mumps uneventfully at two years.

The patient's mother was seventeen years of age at the time of the patient's birth. She had a "goiter" while in school, which disappeared when iodine pills were taken. This, according to her history, was symptomless. While pregnant with this patient, a moderate return of her goiter occurred without symptoms.

The father of the patient, two years older than his wife, was perfectly well. His grandmother's sister had had a goiter. The patient had one brother, aged one year, apparently normal in every respect.

Following are my initial physical findings when the patient was referred by the clinic to the Children's Hospital on Feb. 7, 1933.

The patient was a fairly well-developed, poorly nourished child, apprehensive but cooperating well. Scalp was oily; hair, fine in texture. Ears were negative.

The pupils were round and equal, and reacted well to light and accommodation; extraocular movements, normal. There was marked exophthalmos, no definite lid lag or inability to converge, no strabismus or nystagmus.

The nose was dry, with slight congestion. Teeth were normal; mucous membrane, throat and tonsils, negative. There was no stiffness of the neck; slight postcervical adenitis.

The thyroid was diffusely enlarged (both lobes and isthmus), especially the right lobe which ran well up to the hyoid bone. No nodules were felt. There were thrills over both lobes; loud murmurs were heard over whole. Gland did not seem to run below sternum.

Chest showed good symmetrical expansion with the lungs clear throughout. Heart: point of maximum impulse within nipple; left cardiac border, slightly beyond nipple line. The rate was regular, 168 per minute.

Blood pressure (lying) was 140/60. Systolic blow was heard over the whole precordium, transmitted to the neck. Diastolic murmur was heard at times; no axillary transmission; pulmonic second sound, louder than aortic second.

The abdomen was scaphoid; no solid organs were felt, no tenderness or rigidity. The genitals were those of a normal female infant.

In the extremities a fine tremor was present on movement. The skin was warm and moist. Reflexes were normal and active.

A diagnosis of exophthalmic type of hyperthyroidism was made.

Laboratory findings were: R. B. C. 5,260,000; hemoglobin, 14.5 gm.; W. B. C., 5,500; polymorphs, 41 per cent; S. L., 29 per cent; L. L., 22 per cent; monocytes, 6 per cent; lymphoblasts, 2 per cent; urine, negative; O. T., 0.1 mg., I. D. (H. & B.), negative.

Sugar tolerance: fasting, 78 mg. per cent; peak of 100 at one hour; 88 at two hours; no glycosuria during test. Blood Wassermann was negative.

X-ray examination showed no evidence of tracheal displacement or compression. Thymus was normal. The sella was within normal limits, and there were no shadows suggesting suprarenal tumors.

During an initial period for the purpose of observation and further study, she was allowed a high caloric diet and no medication except small doses of phenobarbital (gr. ¼ t.i.d.). Her temperature varied from 101° to 99° F. (all temperatures rectal), and her pulse rate, from 184 to 120.

On the sixth day her temperature rapidly rose to 106° F., and her pulse, to 160. She vomited, and her stools became quite loose. Nervousness increased. Her voice became much more husky than usual, and she pulled at her neck as though there was a sensation of pressure or tightness there. Her nose began to run; her throat became moderately injected; and her lungs full of fine moist râles. Plainly a crisis had occurred precipitated by the respiratory infection.

Ephedrine drops were used intranasally; 10 per cent glucose was given intravenously, and sedation was increased. Her fever was ineffectually treated by continuous colonic flushes and cold packs. Since Lugol's solution could not be retained by mouth or rectum, intravenous sodium iodide (2 c.c. of 10 per cent solution) was given for three days.

On the tenth day a generalized "luminal" rash appeared, necessitated the discontinuance of barbiturates; sedation was secured henceforth largely by codeine and bromides. By the thirteenth day her temperature had returned to normal and her pulse, to 120. She was then taking 15 gr. of potassium iodide daily by mouth. Her weight had dropped from 27 pounds to 24½ pounds.

The iodide was increased to 20 gr. daily. Her pulse rate dropped gradually to a low of 88 on the eighteenth day. On the nineteenth and twentieth days basal metabolism tests were made. The little patient cooperated well, the rates being plus 21 and plus 23, according to Benedict's tables calculated on height. Her weight at this time was 25 pounds, 5 ounces, and blood pressure, 110/60.

Joint surgical, x-ray, and medical consultation was of the opinion that it would be wiser to follow a conservative course and employ x-ray therapy at this time rather than surgery. The iodide was gradually cut to 1 gr. daily, and three moderately heavy x-ray treatments were given at weekly intervals.

By the time she had received her third x-ray exposure, although her weight had increased to 27 pounds and she looked very well, she was markedly more nervous and emotionally unstable. Her pulse had gradually risen to 160 to 170. Her bowels became loose, and attempts at metabolic readings were exceedingly difficult, readings of plus 163 and plus 165 being obtained on two successive days. Her thyroid was much firmer and definitely nodular.

It was then decided to drop the idea of x-ray therapy, to begin intensive iodine medication again with the expectation of employing surgery if we could put her into proper condition a second time. Lugol's solution was given, the daily dose being gradually increased to 45 minims. Despite this and sodium bromide, 10 gr. every four hours, her pulse would not drop lower than 130. Basal metabolism readings were inaccurate because of her poor cooperation.

After three weeks of intensive iodine medication, when it was seen further improvement was unlikely, bilateral superior pole ligation was performed under nitrous oxide anesthesia by Dr. Dexter N. Richards. The operative report was as follows:

Bilateral incisions were made over both superior poles. The larger lobe was on the right. The vessels were larger there, and this pole extended higher in neck, making vessels more mesial. They were doubly ligated with No. 1 chromic catgut. On the left, the pyramidal lobe was first brought into view, a portion being removed for examination. The left superior pole and vessels were then exposed and vessels again doubly tied with chromic catgut. Subcutaneous tissues were closed with fine plain catgut and skin clips.

Dr. Paul Michael examined the section obtained at operation and reported: "Microscopic sections show portions of thyroid gland in an active state of hyperplasia. There is a small amount of colloid material, probably stored recently due to new growth, and a small amount of excessive fibrosis in the stroma. The essential change observed consists of an adenomatous pattern. The acini are for the most part small and lined by a high cuboidal or high columnar epithelium, resting on a basement membrane which is preserved and giving evidence of marked infolding or feathering. The vessels of the gland are moderately engorged. Diagnosis: hyperplasia of the thyroid gland—very mild involutional changes."

Her postoperative reaction was moderately severe, her temperature going to 103.8° F., and pulse, to 180, with some vomiting and diarrhea. which was easily

controlled and soon stopped. She was kept on Lugol's solution 5 minims t.i.d., and sodium bromide, 5 gr. t.i.d. Her pulse stayed between 120 and 130, and she was much quieter. Yet despite this and a fair appetite her weight decreased to 24 pounds 14 ounces on the fourteenth day postoperatively.

On the twentieth day another acute respiratory infection developed with a second crisis, her temperature rising to 105° and 106° F. for three days with marked increase in nervous symptoms and transient delirium. Following this the Lugol solution was gradually increased to 18 minims t.i.d., her pulse rate still averaging about 130. Coincident with 5 minims of insulin a.c., and the daily quartz light treatments, her weight increased to 27 pounds 12 ounces.

Forty days after her first operation her basal metabolic rate was plus 54. Dr. Richards then performed a right subtotal lobectomy under nitrous oxide and local anesthesia. "Two ounces of ½ per cent novocaine without adrenalin injected for a Kocher type incision, placed a little higher than usual. The usual approach to the

Fig. 1. Fig. 2.

Fig. 1.—Photograph taken on twenty-fifth day when patient was in her primary iodine remission, with a B. M. R. of plus 22, and pulse of 90. X-ray therapy was begun at this time.

Fig. 2.—Photograph taken the day before her thyroidectomy, 40 days after the pole ligation. B. M. R., plus 54; pulse, 130. Gland was much firmer and smaller, but patient was much less cooperative and quiet than when first pictures were taken.

gland without cutting muscles was used. The gland was easily delivered, and there was no excessive bleeding, nor were there any adhesions that could be attributed to x-ray treatment. The gland was much paler than at previous operations, and the superior pole was almost white as a result of the previous ligation. A right subtotal (4/5) lobectomy was performed, bleeding points tied, and muscles very loosely tacked together over a penrose tube drain. The skin was closed with clips; no attempt was made to close the platysma. Her condition was satisfactory all through the operation."

Dr. Paul Michael's pathologic report is as follows:

Gross Findings.—The specimens presented a firm smooth surface. Cut section showed a meaty type of gland presenting marked cellularity and vascularity. There was some increase in fibrous tissue noted.

Microscopic Findings.—Sections showed a cellular thyroid tissue with many plications of the acini. The acini were lined by both high and low cuboidal epithelium with some disintegration of cells. Colloid was mostly pale staining, indicative of recent storage. There was some excess of old fibrous tissue and lymphocytes seen. Diagnosis: involutional hyperplasia of thyroid with mild thyroiditis.

The patient had practically no postoperative reaction. Lugol's solution was gradually cut from 60 to 3 minims daily. By the tenth day her pulse rate had dropped to 80, where it remained. Her metabolism rate two weeks after operation, with the patient only fairly cooperative, was plus 12. She became very quiet; her eyes were markedly less prominent; her appetite improved; and her weight increased to 29 pounds. She was discharged on June 16, 1933, her 129th day in the hospital. She was to be followed in the clinic and a left lobectomy was to be performed later if conditions seemed to indicate its advisability.

She did very well for about five months, gained weight, and continued to have a slow pulse. The Lugol solution had been discontinued by her parents after she was home two months. When seen on Dec. 23, 1933, in the out-patient department she was quiet—almost lethargic. The skin over her body and extremities was dry and scaly. Her upper eyelids were puffy, but there was no falling of hair, and the tongue was not enlarged. Some prominence of the eyes was present. The thyroid showed neither bruit nor thrill, and no enlargement was discernible. There was a definite puffiness and swelling, apparently of the soft tissues, in the left supraclavicular region. Heart rate was from 80 to 84 per minute. Her hands were cold; there was no tremor. Her parents complained that for the last few weeks she had been more irritable than usual and noted some frequency of urination.

Since at that time it was not possible to check her basal metabolic rate or blood cholesterol, she was placed on thyroid extract empirically. After some juggling of dosage she was found by Dr. J. Frug to require about 1/10 gr. of desiccated thyroid substance (Armour or Parke-Davis & Co.). Her pulse remained at 80; the puffiness of eyes and supraclavicular region decreased; her skin was still dry but warm. Her general appearance was good.

In March, 1934, she passed through whooping cough uneventfully, being given Krueger's pertussis endoantigen with good results.

COMMENT

This case typifies the severe form of exophthalmic goiter in childhood. It is illustrative of the uncertainty with which the average physician attempts to treat this condition, simply because it does not occur frequently enough in any one individual's practice to establish estimates of the value and practicability of the various courses of therapy offered.

Mental and physical rest alone are of value but will not control and cure many cases. X-ray therapy is to be considered in the mild cases in which no rapid progress is in place and no emergency likely to occur. Conclusions as to the operative difficulties it may add to subsequent surgery can hardly be drawn from this one case in which none were produced. Surgery seems to be the treatment of choice here as in adults. Iodine preoperatively should always be employed. Preliminary pole ligations are not deemed essential. With present-day anesthesia, proper preoperative and postoperative care, under skilled hands, a child is now to be considered a good operative risk.

Opinion as to the right amount of gland to be removed varies greatly although the trend seems to be toward removing an amount comparable to that removed in the adult—more than was formerly advocated.

McGraw[4] states: "While we doubt that polar ligation of the superior thyroid arteries is a sufficiently radical procedure to insure permanent recession of symptoms, we feel that one should be a shade more conservative in the relative amounts of thyroid tissue left behind at operation, as compared with that left in cases of adult exophthalmic goiter, even risking the necessity of subsequent reoperation, until we have some accurate data on the effect of subtotal thyroidectomy upon human growth and development." Similarly, Means and Richardson[5] write: "Treatment of exophthalmic goiter in children, on account of the milder course, permissibly may be more conservative than in adults. As we noted earlier, the symptoms are less marked, and the course more definitely self-limited. Subtotal thyroidectomy, therefore, probably will rarely be necessary, and there are certain obvious reasons why it is less desirable to deprive a growing child of five-sixths of his thyroid than an adult. X-ray would seem to be the method of choice with thyroidectomy only in cases that did not show a satisfactory improvement after a reasonable length of time (three or four months)."

On the other hand Beilby and Carleton[6] state: "Experience may teach us that thyroid tissue regenerates more rapidly in the young individual and that we can safely remove an amount at least proportionate to the older patient."

Crile[7] expresses the opinion that "the younger patient requires the removal of more than the older one . . . the larger the gland the more mass is left."

The results obtained in the case here presented, i.e., mild hypothyroidism following a hemi-subtotal thyroidectomy, may be explained as the result of the additional repression of gland activity caused by the preoperative x-ray therapy and the superior pole ligation.

One well-established statement is ably verified by this case, "Employ iodine to obtain a remission of symptoms and that only preoperatively." Hope that the iodine remission will persist and further treatment be unnecessary is like hiding in one's straw house to avoid the wolf.

SUMMARY

A case is presented of a two-and-one-half-year-old child with severe exophthalmic goiter, whose symptoms began when she was six months old. The benefits of an iodine remission were lost (and never completely regained) in order to employ x-ray instead of surgery. When this failed to halt the progress of the condition, bilateral superior pole ligation was performed and later hemi-subtotal (⅘) thyroidectomy. Mild hypothyroidism resulted.

NOTE: A child of a subsequent pregnancy of the patient's mother is said to show symptoms similar to the sister reported here.

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CLINICAL RECORD AND POSTMORTEM PATHOLOGY OF DIABETIC CHILDREN

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DIABETES in children is no longer a clinical curiosity. Furthermore, with the advent of insulin, the ranks of diabetic children in this country are swelling rapidly each year at the rate of about 1,000. On the whole, the progress of these children is good, and it is better with each succeeding year of their diabetes. The first year of their diabetes is the critical year, and highest mortality rate among diabetic children occurs during this time. This is not due to the fact that the inherent nature of diabetes is any different in the first year than in the later years, but rather to the fact that the mother and the family doctor are facing a problem which is new to them. They either learn to handle it reasonably well and meet adequately the complications which may occur, or else they fail in some way or other, and death is the result. The next two years of diabetes of a child are still fraught with danger, owing to the same factors. After three years the accidents happen less frequently, as by that time the mother has learned her problem well, and she is accustomed to meeting the various emergencies as they arise.

Thus among 214 diabetic children under my care (from one to twenty years of age) the mortality during the first year of diabetes was 39.2 per cent of the total mortality, which was 13 per cent;[1] this includes two years in the preinsulin era, and the deaths among patients who had diabetes for three years or less constituted 64.2 per cent, of the total number of fatalities. These figures show that it behooves us to exert a special effort the first year in every new case of diabetes in a child and to maintain close supervision during this time. Accidents will always occur, but they are apt to be much more frequent at the beginning.

Diabetes can occur at any time of a child's life. In Table I, I have charted cases gleaned from the literature. All seventy-eight of these patients are under one year of age. There are six cases of congenital diabetes and four more which were discovered within a few days after birth and could thus be classified as congenital. This speaks strongly for heredity, for at this age other factors can certainly be ruled out. Heredity is an important factor in the etiology of diabetes in children. Thus among my own group of Jewish children, there was a familial history of diabetes in 30 per cent; in Joslin's series in 44 per cent and in Priesel Wagner's in 43 per cent. In the non-Jewish children heredity

TABLE 1

DIABETES MELLITUS IN SEVENTY-EIGHT INFANTS UNDER ONE YEAR

NEWBORN		FEW DAYS		DAYS OLD							
				21		90		120		135	
Morrison	1	Kitselle	1	Labbé	1	Nichuas	1	Schippers	1	Kochmann	1
LaSalle	1	Garnerus	1			Bell	1				
Ambard	1	Langstein	1			Caron	1				
Feldmann	1	Schretter and Nevinny	1			Dreyfus, et al.	1				
Osler	1					Knox	1				
Schretter and Nevinny	1					Heiberg	1				
						Arndt and Walker	1				
						Wegeli	2				
	6		4		1		9		1		1
150		180		240		300		330		Under one year	
Ashby	1	Young	1	DeLange	1	Burghard	1	Shelley	1	Busch	1
Orloff	1	Langstein	1	Rossbach	1	Tavaria	1	Major and Curran	1	Stern	6
Caillot	1	Eaton-Woods	1	Hagenbach	1			Lenstrup	1	Wegeli	2
				Schippers	1					Joslin, et al.	3
				Knox	1					Offergeld and Roman	1
				Langstein	1					Feldmann	1
				LaSalle	1					Neumann	1
				Dreyfuss, et al.	1					Ghon	1
				Kochmann	1					Haüner	1
				Wegeli	1					Ashby	1
										DeLange	1
										Arndt and Welcher	1
										Ramsey	1
										Gingsberg	1
										Lenstrop	1
										Morton	1
										Letchfield	1
										Shelley	1
										LaSalle	4
										Labbé	3
										Heiberg	2
	3		3		10		2		3		35

was a factor in my own cases in 17.9 per cent and in Priesel Wagner's cases in 21 per cent. This means an increase in the heredity factor in the Jewish group of 101 per cent.

Infection seems to stand next in line as an etiologic factor. This is by no means a new idea, for acute infections as the cause of some cases of diabetes was suggested first by Aretaeus of Cappadocia[2] (A.D. 30 to 90) who lived under the Emperor Nero. I have reported[3] eleven children in whom the onset of diabetes was within the first ten days after various infections (some as early as second and third day), seven in whom the onset of diabetes was from eleven to twenty days after, and thirteen, from twenty-one to thirty days after. I have gathered from the literature ninety-eight cases (including my own) in which the diabetes followed infectious diseases. The possibility of diabetes developing after acute infectious diseases must be kept constantly in mind, and for three to five weeks following any infectious disease, the physician should be on the lookout for glycosuria. The whole problem of the treatment of diabetes hinges upon its early discovery, before too much damage has been wrought to the pancreas.

Over a period of fourteen years, 1920 to 1934, a period which goes back two years into the preinsulin era, I have had under my care 214 diabetic children between the ages of one and twenty years. Of these, 186, or 87 per cent, are living, and twenty-eight, or 13 per cent, are dead. An analysis of the twenty-eight cases in which death occurred is given in Table II.

Of this group four came to autopsy, and I am recording these cases in detail in this communication. In one case adrenal denervation had been performed, and the patient died of adrenal insufficiency at the age of twenty-one years, having had diabetes less than one year. The diabetes had been secondary to hyperthyroidism. One patient died in coma at the age of ten years, having had diabetes for six years. One patient had acute bilateral pulmonary tuberculosis and died at the age of twenty-one, having had diabetes for six years. One girl, aged sixteen years, who had diabetes for eight years, died in coma and had fatty degeneration of the liver. She was first seen *in extremis* and died within an hour after her arrival.

Allen's dictum, "Without pancreatitis there is no diabetes," seems to hold when one studies the pathologic reports in the literature. Some cases are reported in which no changes in the islands were found, but these represent largely pathologic studies in which special staining methods had not been employed. Consequently, we must take this fact into consideration. Even in the presence of negative findings, a functional change in the islands is not ruled out, a fact which Allen pointed out many years ago. The closer one studies any problem the more evidence he finds; this dictum can be applied to the pathologic study of diabetes.

TABLE II

MORTALITY OF 28 CHILDREN IN A SERIES OF 214 DIABETIC CHILDREN*

NO.	AGE IN YEARS		SEX		CAUSE OF DEATH								DURATION OF DIABETES IN YEARS
	ONSET	DEATH	M.	F.	COMA	TUBERCULOSIS	ADRENAL DENERVATION	KILLED IN ACCIDENT	APPENDECTOMY	SEPTICEMIA	OTITIS MEDIA	UREMIC COMA	
1	16	19	○		○								3.0
2	18	23	○			○							5.0
3	20	21	○				○ Pm.						1.0
4	14	18	○						○				4.0
5	14	14	○		○								0.1
6	11	11	○		○								0.1
7	4	10	○										6.0
8	17	23		○	○								6.0
9	14	16	○		○								2.0
10	7	7	○		○								0.1
11	5	7	○		○								2.0
12	1	1	○		○								0.3
13	5	6	○					○					1.0
14	10	11	○		○								1.0
15	7	11	○						○				4.0
16	12	12	○		○								0.5
17	4	10	○		○ Pm.								6.0
18	12	13	○		○								1.0
19	4	11	○							○			7.0
20	19	20		○	○								1.0
21	3	4		○	○								1.0
22	15	21		○		○ Pm.							6.0
23	18	18		○							○		0.5
24	8	16		○	○ Pm.								8.0
25	17	17		○	○								0.0
26	14	15		○	○								1.0
27	12	20		○		○							8.0
28	18	18		○								○	0.2
Total			18	10	18	3	1	1	2	1	1	1	

Total deaths 28. Of these I took care of 5. Cause of death of these: Case 3, adrenal insufficiency after denervation; Case 5, coma, preinsulin era; Case 6, coma, preinsulin era, brought in last stage; Case 24, coma, brought in last stage; Case 25, coma, died one hour after reaching hospital.

*Includes preinsulin era, ages one to twenty years.
P.m—Postmortem.

Note the frequent and varied changes in which Shields Warren[4] finds in his pathologic studies in diabetes. With all his reservation and his characteristic thoroughness the evidence which he brings out seems quite marked.

Table III presents the pathologic findings at postmortem of twenty-four children as reported in the literature by various authors. In only two of these no changes in the pancreas were reported.

In the study of the gross and the minute changes in autopsy specimens of the pancreas from persons other than diabetic patients, according to Keilty,[5] many different pictures are encountered which are principally the loss of structure, true atrophy with fatty replacement, calcification,

TABLE III

AUTOPSY REPORTS ON DIABETIC CHILDREN

NO.	AGE IN YR.	NO ISLANDS DIMINISHED	ISLANDS DIMINISHED IN SIZE	FIBROSIS, ATROPHY, SCLEROSIS OF PANCREAS	HYALINE DEGENER. OF ISLANDS	HYDROPIC DEGENER. OF ISLANDS	NECROSIS OF PANCREAS	CONGEN. ABSENCE OF PANCREAS	NO ISLANDS	NO CHANGE	AUTHOR
1	0.25	○									Heiberg
2	0.66	○									Kochmann
3	0.75	○	○								Knox
4	1.25	○									Heiberg
5	3.00			○	○	○					Martins
6	4.00						○				Anderson
7	4.50	○		○							Heiberg
8	4.50	○									Heiberg
9	5.00	○									Heiberg
10	5.00	○		○							Heiberg
11	6.00	○									Bihlmeyer
12	7.00			○							Phillip
13	10.00			○					○		John
14	11.00			○							Frontini
15	12.00			○	○	○					Martins
16	14.00							○			Ghon
17	15.00									○	Nobecourt
18	15.00			○	○	○					Martins
19	16.00		○	○							John
20	16.00			○	○	○					Martin
21	16.00			○							Lindblom
22	16.00	○		○							Lancereaux
23	20.00		○	○							John
24	21.00									○	John

passive congestion, arteriosclerotic changes with perivascular fibrosis, interlobular, intralobular, interacinal and intraacinar fibrosis with hyalinization and lymphocytosis and variations in the size and number of cells of the islands of Langerhans. The island changes in non-diabetics are not so marked or so striking as in the diabetics. In addition to these, the pancreas is the seat of acute inflammation, specific inflammations, tuberculosis and syphilis, and congenital deficiencies with cysts and neoplasms.

Opie[6] sums up the work of R. L. Cecil, a study of ninety cases of diabetes as is shown in Table IV.

In seventy-nine cases, or 88 per cent of the ninety cases of diabetes, Cecil found lesions of the islands. Hydropic degeneration was not

TABLE IV

Interacinar pancreatitis	
With sclerosis of the islands of Langerhans	39
With hyaline degeneration of the islands of Langerhans	19
With sclerosis of the islands of Langerhans and lipomatosis	2
With hyaline degeneration of the islands of Langerhans and lipomatosis	1
With sclerosis of the islands of Langerhans and hemachromatosis	2
Total	63
Interlobular pancreatitis	
With sclerosis of islands of Langerhans	4
Total	4
Parenchyma normal; lesions of islands of Langerhans	
Sclerosis of islands of Langerhans	4
Hyaline degeneration of islands of Langerhans	7
Infiltration of leucocytes of islands of Langerhans	1
Total	12
Pancreas normal in structure	
Pancreas, small; and islands of Langerhans, few	2
Islands of Langerhans, few	3
No abnormality noted	6
Total	11

ruled out, as the refined methods of fixation and granular staining of Lane and Bensley were presumably not carried out in this series.

Keilty states that in his experience the finding of a small pancreas, which presumably has a decreased number of islets, is the most common and striking finding in cases of diabetes. Whether this is congenital or a part of a general atrophic change, whether secondary or primary to diabetes, may be still open to argument.

Hoehn[7] studied autopsy records of twenty-one cases of diabetes and found island changes in all. Conroy[8] studied twelve cases with serial blocks of tissue and showed a reduction of insular tissue of 50 per cent. Every case showed qualitative changes in the islands, hyalinization and fibrosis. These changes were not so noticeable in nondiabetic controls.

Allen[9] reviewed a total of 570 cases in which the pancreas was studied. There were abnormalities in 48 per cent of the 549 individuals who were nondiabetic; he found abnormalities in 100 per cent in the twenty-one who were clinically diabetic.

TABLE V

COMPARATIVE PATHOLOGIC REPORTS IN ADULTS AND IN CHILDREN

	TOTAL CASES	NO CHANGE IN PANCREAS	PER CENT	DEFINITE CHANGE IN PANCREAS	PER CENT
Children	24	1	4	23	96
Adults	364	18	5	346	95

I have gathered from the literature a record of the microscopic examinations in 388 cases of diabetes. Of these, 364 were in adults and twenty-four in children. Reports of the findings in these two groups are shown in Table V.

CASE REPORTS

CASE 1.—A young man, aged twenty years, an automobile painter, was admitted on the surgical service Oct. 13, 1930. He complained of loss of weight and nervousness, polyuria and frequency. About six months before, he had begun to lose weight. His endurance was poor; he felt tired and run down. About four weeks before he had begun to pass large amounts of urine and to drink large quantities of water. A diagnosis of diabetes had been made, and he had stayed in a hospital for ten days with no improvement. After leaving the hospital, he noticed that he was becoming more nervous; he developed a tremor of the hands; and he perspired a great deal and felt drowsy most of the time. He had a voracious appetite. The family history was negative.

His weight at this time was 103 pounds; height, 5 feet 6 inches; his best weight had been 140 pounds. His blood sugar content at this time was 206 mg. per cent, four hours after eating. The blood urea content was 36 mg. per cent. There was no sugar in the urine and but a faint trace of albumin. Physical examination was negative with the exception of the tremor of the hands. The basal metabolic rate was plus 20 per cent; he presented the typical picture of hyperthyroidism. On small dosages of insulin the blood sugar fluctuated at a low level on a 3,000 calorie diet (Chart 1). A few days later a glucose tolerance test revealed a frankly diabetic curve. After a short stay in the hospital he was sent home on the 3,000 calorie diet and 5 units of insulin, which had to be increased to a dosage of 4-0-4, then to 8-0-8, and finally to 15-0-15 units.

He returned in a little over a month during which time he had gained 12 pounds and was generally improved. His fasting blood sugar at this time was 120. A basal metabolic rate taken on the third day was plus 32 per cent; the glucose tolerance test was repeated and gave the same type of curve as before. With the increased metabolism, the insulin requirement increased to 20-20-20 units per day. Lugol's solution was administered and gradually reduced the basal rate. The blood sugar level, in spite of the increase in insulin, was considerably higher now. In two weeks denervation of the left adrenal was performed in an effort to control the hyperthyroidism and diabetes. Immediately following this for four days, the level of the blood sugar rose. The insulin had to be increased to 15-15-15-15 units per day. Two weeks after the denervation the patient returned home, the insulin dosage being 15-15-15 units.

He returned to the hospital in three weeks. His blood sugar level at this time was higher, fluctuating at about 230 mg. per cent. The basal metabolic rate had risen to plus 43 per cent. On the third day after his return, the second adrenal gland was denervated; on the second day following the operation, he died. His death looked like that caused by thyroid crisis; there were râles scattered throughout both lungs. Tracheotomy was performed, and an oxygen tent used, without improvement of symptoms.

The postmortem examination cleared up the complex clinical picture. The first adrenal was fibrosed, the gland atrophied—thus not functioning. The second adrenal showed multiple thrombi in the vessels; the medulla was hemorrhagic, thus also not functioning. The man died of acute adrenal insufficiency.

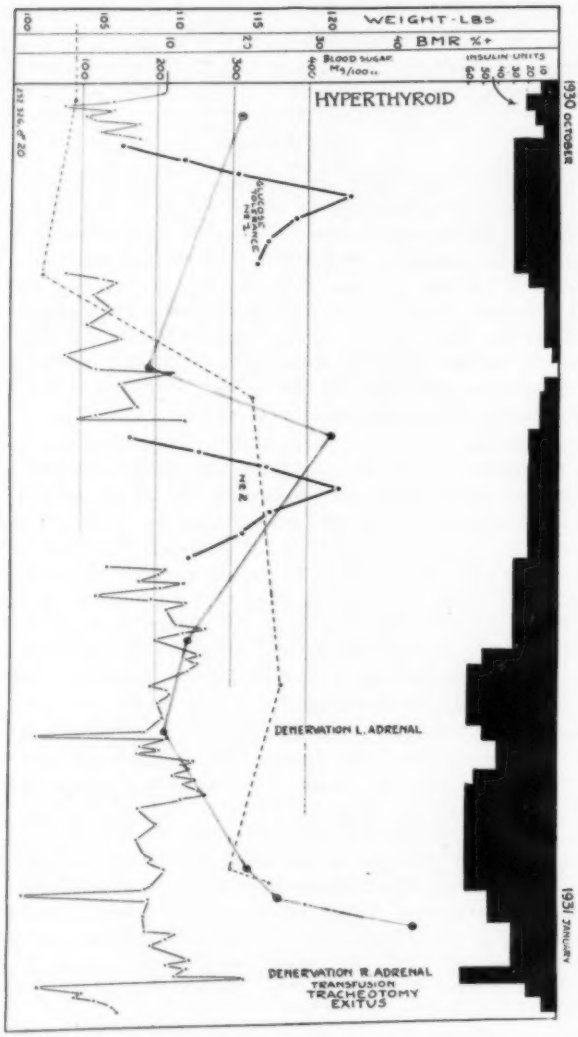

Chart 1.—Progress in Case 1. Youth, twenty years old, with diabetes and hyperthyroidism died of acute adrenal insufficiency following bilateral adrenal denervation.

Pathologic Report

Adrenals.—The right adrenal was imbedded in a large quantity of formed adhesions and fibrofatty tissue. It was large and on section showed, in the lower pole, multiple thrombi in the vessels. The cortex was apparently intact, but the medulla was quite hemorrhagic and in several areas contained a large amount of old, clotted blood. There was poor differentiation between cortex and medulla, and in one area cloudiness suggesting early necrosis.

The left adrenal was imbedded in a mass of white, old scars. A portion of the gland was atrophied. There was very little substance remaining, either cortical or medullar. The portion, however, that did remain showed fair differentiation.

Sections of right adrenal showed extensive, recent hemorrhage, thrombosis of vessels and necrosis of adrenal tissue. There were only a few, relatively small areas of comparatively normal cortical tissue present. The surrounding fat contained a large amount of blood, fibrin, and leucocytes.

Sections of the left adrenal showed fairly large areas of comparatively normal medullary tissue and scattered areas of somewhat altered cortical tissue. The capsule of the adrenal and surrounding tissues showed great increase of fairly dense, collagenous, fibrous tissue, in which were many lymphocytes, plasma cells, and a few leucocytes and phagocytes containing blood pigment. A large artery, apparently belonging to the adrenal, showed obliterating endarteritis. There was a large sympathetic ganglion in the section and a small hyperplastic lymph node.

Another section of this adrenal, probably at the opposite end, showed large areas of necrosis and degeneration of a greater portion of the cortical tissue, with only a small area of comparatively well-preserved cortex near one end. There was extensive fibrosis in and around the adrenal.

Thyroid.—The thyroid weighed 50 gm. Both lobes were slightly enlarged. The left superior and right inferior parathyroids were present. Section of each lobe showed a slightly hyperplastic gland with a great amount of lymphoid. It was present in large and small, discrete areas. There was considerable colloid; there were no adenomas.

Sections showed goiter, hyperplastic, moderate (involuting) with very little increase of stroma, no lymphoid tissue, and no adenomas. One section showed a normal parathyroid.

Thymus.—The thymus weighed 50 gm. It measured $12 \times 6 \times 2$ cm. and was greatly enlarged, made up of two lobes. It was soft, white, and fairly friable. Sections of the two lobes showed a white, glandular structure, with fibrous tissue trabeculae.

Section showed hyperplastic lymphoid tissue with numerous small and large Hassall's corpuscles, some of which apparently were undergoing a granular or hyaline degeneration.

Liver.—The liver weighed 1,380 gm. The right lobe measured $18 \times 20 \times 9$ cm., and the left lobe, $8 \times 17 \times 6$ cm. The contour was normal; the edge was fairly sharp; and the capsule stripped readily. The vena cava and portal veins were clear. Section of liver showed fairly distinct lobules. The central veins were prominent and patent. Several of the smaller hepatic arteries showed a cloudy, milky chylelike substance. There was bile present in several of the smaller bile ducts. The cut section had a rather cloudy, homogeneous appearance. There were no definite tumor nodules and no evidence of focal necrosis.

Sections of the liver showed congestion of vessels, no increase of fibrous tissue. The liver lobules and cords were practically normal except for numerous, small vacuoles in a large number of liver cells in many lobules, probably fat. In addition, there were localized areas of larger fat globules in various sections. The biliary ducts appeared normal.

Pancreas.—The pancreas weighed 90 gm. and measured 17 cm. in length. At the head it measured 5×3 cm., and at the tail, 3.5×2.5 cm. Cut section showed no gross abnormality. There was no fibrous or fatty infiltration of any portion.

The microscopic examination showed a definite increase of interlobular fibrous tissue and increased fibrous tissue around the blood vessels and the larger pancreatic ducts. There was very little fat in the pancreas. The lobules, generally, were well

preserved. The islet tissue, generally, was inconspicuous. In some sections, particularly in the region of the head, there were a few normal-sized and larger histologically normal islands. A few islands showed a moderate degree of atrophy and fibrosis, and an occasional lobule showed atrophy and fibrosis.

CASE 2.—The patient, a boy, who was ten years old in 1930 when first seen, had had diabetes for six years. Diabetes had appeared a few days after an infection, whooping cough and Vincent's angina. He was on a special diet and was taking 25 units of insulin once a day. He had been in coma several times and had had measles and chickenpox during the course of the diabetes. He also had had a mastoid operation three years before. Briefly, his condition was not well con-

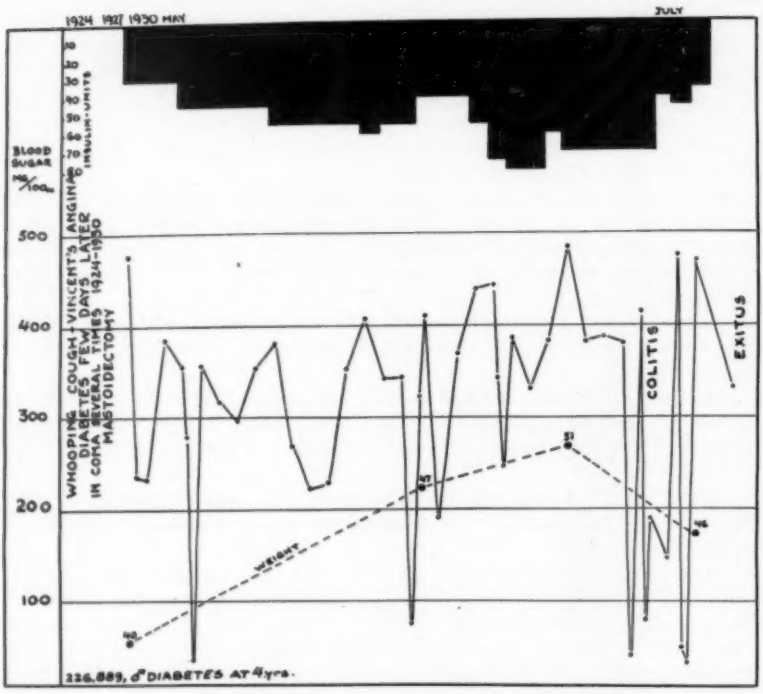

Chart 2.—Progress in Case 2. Boy developed diabetes at the age of four years following a severe throat infection and died six years later in coma following another infection, colitis.

trolled, and he was gradually becoming more severely diabetic. Inquiries concerning the family history elicited the fact that a maternal aunt and two cousins had diabetes.

When he was first seen, May 22, 1930, his blood sugar content was 476 (Chart 2); he had pronounced glycosuria. He was given an 1,800-calorie diet and 10-10-10 units of insulin, this dosage being increased to 15-15-15 and then to 15-15-15-15. His diet, because of his undernutrition, was raised to 2,500 calories, and marked gain in weight resulted. The figures in Chart 2 represent fasting blood sugar contents, thus high in values; his twenty-four-hour sugar output at the beginning was fluctuating from 5 to 50 gm. He was discharged from the hospital in five weeks, on a 2,000 calorie diet and 20-10-10-10 units of insulin.

Ten days later he developed fever and diarrhea, followed by acidosis. As he lived in a small town without facilities for hospital care, he died on the fourth day.

This child had had severe diabetes for six years and had lost much of his sugar tolerance. His blood sugar was high, and the insulin could not be raised above the amounts mentioned because he suffered severe insulin reactions. He was losing, on the average, about 20 gm. of sugar per day and getting from 100 to 120 gm. of carbohydrate. A diabetic child who has a severe type of diabetes is always a difficult problem, especially if infections occur, for there is little to fall back on. Acidosis develops quickly; liver glycogen reserves are small or nonexistent; thus coma follows quickly the onset of acidosis. If there is much delay in getting such a child to a hospital, death occurs in a short time, as in this case. Though this boy was ten years old, his stature was that of a six year old. He gained much weight and improved in every way during the five weeks of his hospital stay, yet the type of response seen usually in a child in the early stages of diabetes was lacking. A patient of this type requires much insulin, and, while one reaches finally a state of equilibrium, such a state remains stationary with little or no increase of tolerance with time. In other words, in such a late state of diabetes, the damage done is permanent, and the process is irreversible.

The postmortem examination showed a small, soft pinkish gray spleen. Both kidneys showed an adherent capsule and little congestion in the cortex. The liver was small, soft, pale red, and cut with little resistance; the cut surface was beefy red, bleeding moderately. The spigelian lobe was unusually large. The pancreas was small and firm. The gallbladder was somewhat enlarged, adherent to the under surface of the liver—ducts patent. The heart was of average size. The thymus was not enlarged.

The microscopic examination was as follows: The glomeruli of the kidneys were unusually large, their capillaries packed with red cells. Renal tubules, especially their proximal portion, were lined with swollen and cloudy cells. Some were filled with hyaline material. There was marked increase in the interstitial connective tissue. The blood vessels were distinctly thickened and fibrous.

The pancreas showed marked perilobular fibrosis. The small blood vessels exhibited marked fibrosis and thickening. No recognizable islands of Langerhans could be found.

Adrenals showed marked autolysis, considerable deposits of pigment, and red cells; the spleen was markedly congested.

Case 3.—A girl, sixteen years of age, when seen first in 1926, nine months after diabetes had developed following influenza and pneumonia. Hers was a typical case of fully developed, uncontrolled diabetes. The patient's weight had dropped from 115 to 86 pounds in six months. She was very nervous and suffered from nocturia, thirst, marked polyphagia, and "bloating" of the stomach. She had been told she had appendicitis and ovarian trouble.

While her diabetes, according to the history, developed in January, it was not diagnosed until June, when she had the symptoms mentioned. Following the influenza, the family physician gave her an increased diet in an effort to help her regain her losing weight and strength. Even after the diagnosis of diabetes was made, six months later, she was given no insulin, and she did not pay much attention to her diet.

When I saw her on Oct. 6, 1926 (Chart 3), she presented the typical picture of an emaciated diabetic youngster. She had a blood sugar content of 357, acetonemia, and lipemia. The urine contained 3.3 per cent sugar, heavy acetone, and diacetic acid. The plasma carbon dioxide was 23.3 mm.

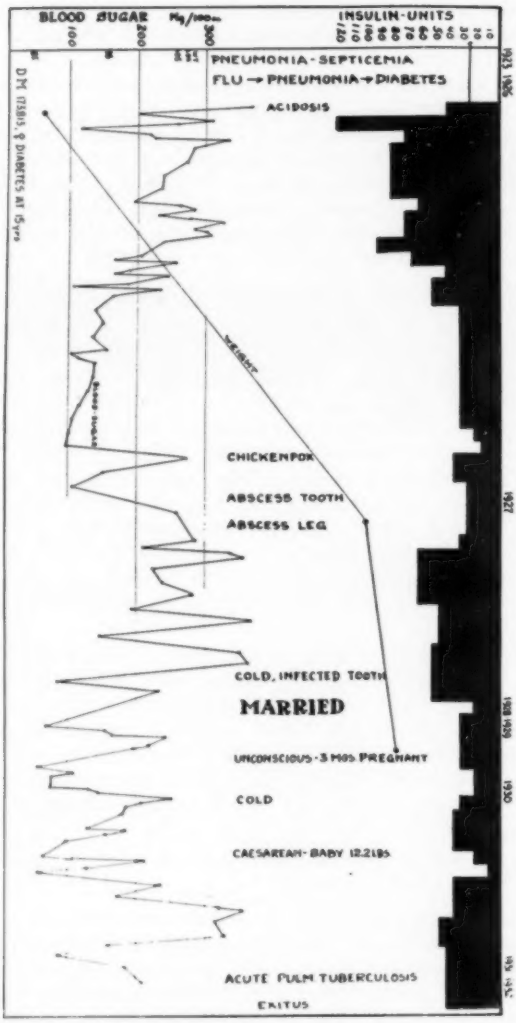

Chart 3.—Progress in Case 3. Girl developed diabetes at the age of fifteen years, married at seventeen, gave birth to a healthy baby, and died two years later of acute pulmonary tuberculosis.

On a 1,600-calorie diet containing 70 gm. of carbohydrate and as much as 120 units insulin per day, it took nine days to reduce the lipemia.

She made good progress and was discharged from the hospital in three weeks on insulin 10-10-10. In five months her weight increased from 86 to 137.25 pounds; she was a tall girl. She left the hospital with normal blood sugar and sugar-free urine. Chickenpox, the first upset, caused a considerable rise of blood sugar; next was an abscessed tooth, then a leg abscess. Insulin had to be increased, and finally when a better control of her condition had been achieved, in September, 1927, she

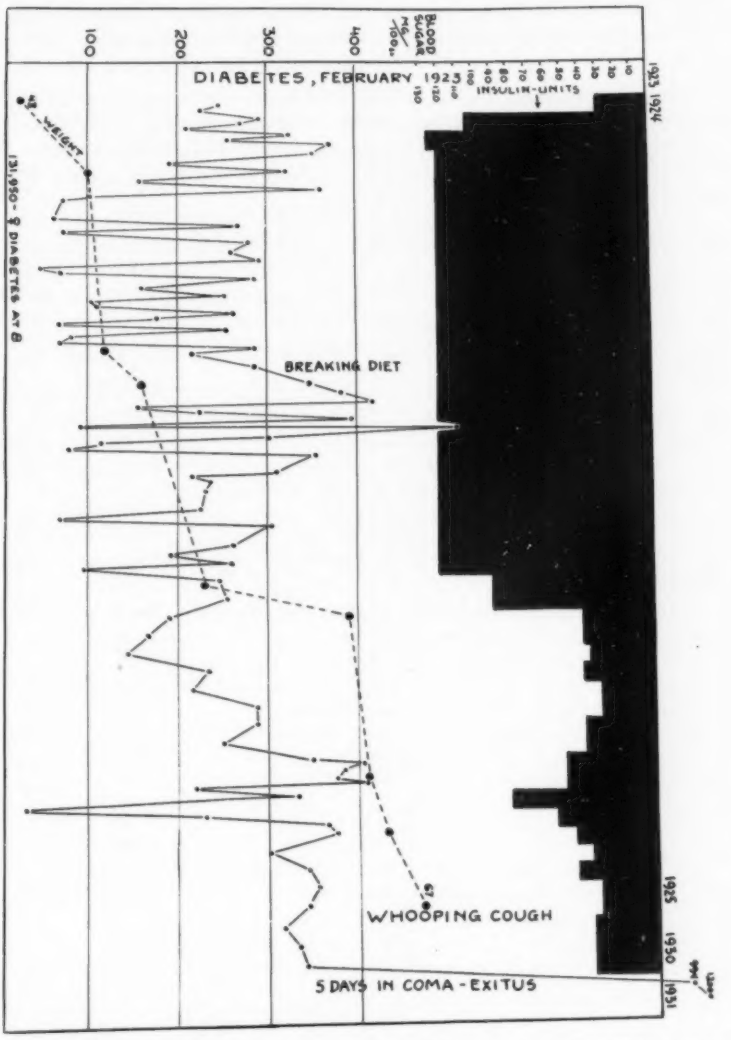

Chart 4.—Progress in Case 4. Girl developed diabetes at the age of eight years and died eight years later in coma due to the discontinuation of insulin. This child had a large fatty liver.

married. Pregnancy soon followed. During the latter part of her pregnancy her diabetic condition improved considerably. Had it not been for the intervening infection which necessitated temporary insulin increase, the record would be even more striking. She was delivered of a 12.2 pound healthy baby girl by a cesarean section at term. Note that the insulin requirement of the mother increased after delivery. Two years later she died of disseminated pulmonary tuberculosis.

The postmortem diagnosis was bilateral chronic ulcerative pulmonary tuberculosis; chronic fibrous pleurisy, bilateral; diabetes mellitus (the islands were well defined); the liver showed advanced cloudy swelling and some fatty degeneration.

CASE 4.—The patient, a girl, had diabetes at the age of eight years. Of the childhood diseases she had measles, chickenpox, mumps, grippe, and tonsillitis. The onset of diabetes following tonsillitis showed the classical symptomatology. Her family physician prescribed various diets, but she did not get along well. After a year of this, she was placed under my care.

At the time I saw her she had 5 per cent of sugar in the urine and a blood sugar content of 245 (Chart 4). Her weight was 43.75 pounds. She was placed on an 1,800-calorie diet, 80 gm. carbohydrate, and as much as 120 units of insulin per day. There was a marked fluctuation of blood sugar. She was discharged from the hospital in four weeks on a 2,000-calorie diet, 120 gm. carbohydrate, and 30-30-30 units of insulin. On this routine she was excreting from 2 to 6 gm. sugar in twenty-four hours.

To start with, we were dealing with a severe case of diabetes of one year's standing. The patient had a protruding abdomen and markedly enlarged liver. This is a sign which I have learned to regard as unfavorable, for diabetic patients with a fatty liver do not do well; their metabolism has been deranged far beyond a disturbance of carbohydrate metabolism—it involves metabolism at large.

In two months, because she started to have insulin reactions, her insulin had to be cut down considerably for a period of about six months; then it had to be increased. Her weight during this time increased, and except for the protruding abdomen, she looked well.

In January, 1931, she developed a cold. Acidosis developed; her family physician cut out all insulin because of vomiting. She went into a coma and was brought into the hospital on the fourth day. Her blood sugar at 12:30 A.M. was 994; CO_2, 9.9; urea, 60. Twenty units of insulin were given intravenously; at 1:00 P.M. her blood sugar was 1,200, and she died at 1:20 P.M.

Clinically she had been making a slow improvement, but there were no changes in the size of the liver. Acidosis resulting in coma, which was badly managed, ended her eight years of diabetes.

The postmortem showed the following:

1. Atrophy of the islands of Langerhans; pancreas 37 gm.
2. Fatty degeneration of the liver, which weighed 2,250 gm.
3. Subacute and chronic interstitial myocarditis.
4. Acute nephrosis.
5. Persistent thymus (normal for the age).
6. Multiple follicular cysts of the ovaries.

DISCUSSION

In a study of 9,000 cases of thyroid disease, I found 207 cases, or 2.3 per cent, of permanent diabetes.[10] Such an incidence of diabetes is higher than the incidence generally. The question one cannot answer is: Was the hyperthyroidism, the increased metabolism, and therefore the increased consumption of food which accompanies it the sole cause of diabetes, or was it merely the precipitating factor, superimposed on a diabetic "anlage"? I am inclined to think the latter supposition correct but, of course, cannot be sure. Be that as it may, a pathologic explanation for diabetes is found in the pancreas itself—a

diminished number of islands, atrophy, and fibrosis—all of which presuppose a diminished insulogenic function in the presence of a demand for an increased function (see Case 1).

In one of the patients (Case 2) diabetes resulted from an infection—whooping cough—which was followed by Vincent's angina of the throat. This history is strongly suggestive of the infections affecting the pancreas. I have studied a group of children whose diabetes evolved in a period from two to thirty days following such infections as colds, influenza, measles, mumps, dysentery, pneumonia, tonsillitis, boils, glandular fever, pyelitis, and jaundice.

We know clinically that such infections do affect the pancreas since diabetes follows where there was no diabetes before. Pathologically a good illustration is offered among others in the case reported by Lemoine and Lapasset,[11] who report a case of an Algerian soldier admitted to the hospital in 1902 with an attack of mumps. On the tenth day he had fever and chills and a swollen testicle. On the fourteenth day the temperature was normal, and the patient was discharged. On the fifteenth day he felt bad and vomited. The temperature was normal, but he had an epigastric tenderness, and the spleen was palpable. He became jaundiced; the vomiting increased; and on the sixteenth day he died. The postmortem examination showed a swollen and edematous gallbladder. The pancreas was three times its normal size (weight 190 gm.), edematous, and congested; the lymph glands were swollen. Histologically the acini were enlarged; the islands, diminished.

CONCLUSION

Four cases of diabetes in childhood and adolescence came to autopsy. Of the four, one followed hyperthyroidism, and three followed infection. One patient died of adrenal insufficiency, two of coma, and one of tuberculosis. Diabetes was present less than a year in the first patient, six years in the next two, and eight years in the fourth. Three of these showed pathologic changes in the pancreas and in the liver.

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PERIMENINGITIS

Staphylococcus Septicemia Complicated by Osteomyelitis of the Second Lumbar Vertebra

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EPIDURAL abscess and a complicating meningitis as a result of blood stream infection are now accepted as a distinct entity. Schmalz,[1] Pincoffs,[2] Dandy,[3] Gay[4] and Rosamond[5] have all reported cases.

Despite its definite symptomatology which permits of accurate diagnosis, the number of recoveries reported are few, and most of these patients have had residual paralyses and serious dysfunction because of the location of the infection.

The following case is of interest because of the complete recovery after such a serious illness.

The case reported is primarily a case of staphylococcus septicemia which resulted in an osteomyelitis of the second lumbar vertebra and was further complicated by an involvement of the spinal cord and meninges with a resulting perimeningitis.

Osteomyelitis of the vertebrae is decidedly uncommon, and perimeningitis is still more so. The mortality in cases such as these is high. Because of the successful outcome the case reported here, an outline of the treatment is included.

L. L., aged fourteen years, was admitted to the Children's Hospital of Michigan on Sept. 11, 1931, with the complaint of fever and pain in the back.

On Sept. 2, 1931, the child complained of pain in the back. The following days she did not eat well and complained of her back from time to time. On September 5, the pain became more severe and radiated to both flanks; however, as long as she was quiet, the pain was not severe. On September 6, she was taken in an automobile to a physician and walked into his office. She walked with a stiff back and complained that motion increased the pain. The following day her temperature rose to 103° F., and she was delirious. September 8 and 9, her condition continued to become worse. She was irrational from time to time and complained of excruciating pain upon the slightest motion.

Physicial examination Sept. 10, 1931, at the time of admission to the hospital revealed a white female child who appeared acutely ill. There was generalized hyperesthesia. Examination of the ears, eyes, nose, and throat was negative. The neck was held rigidly although there was no opisthotonos. The chest revealed a normal heart and lungs. The abdomen was flat and symmetrical. There were no palpable masses. Tenderness or rigidity were not present. The knees were flexed, and there was pain upon extension of the legs. The knee jerks were present. The

From the Children's Hospital of Michigan.

Babinski sign was positive bilaterally, and the Bruzinski sign was positive. Examination of the back showed marked tenderness in the lumbar region. There was no particular localization of the tenderness, and swelling was not present. A lumbar puncture showed a cloudy fluid, xanthrochromic, with 482 cells, practically all polymorphonuclear. The smears showed gram-positive cocci morphologically identical with staphylococci. A cisternal puncture at the same time showed a clear fluid with 138 cells, 50 per cent polymorphs, and the smear and culture were negative. Blood count: 70 per cent hemoglobin; 4,390,000, R. B. C.; 7,250, W. B. C., with 66 per cent polymorphonuclear neutrophil leucocytes. Blood culture was positive for staphylococci. The urine was negative. The Wassermann and tuberculin tests were negative.

On September 12, her condition was unchanged. September 13, she complained of pain in her left wrist. Roentgenograms of the spine showed what was thought to be an epiphysitis involving all of the dorsal and lumbar segments. The next day the blood count showed 31,900 W.B.C. and 88 per cent P.M.N. There was a marked swelling in the region of the second lumbar vertebra. September 15, she was given a transfusion of 510 c.c. of whole blood by the direct method. Two cubic centimeters of staphylococcus bacteriophage was given subcutaneously daily. The following day, a localized abscess appeared on the left ankle. The blood cultures of September 12, 15, 16, 18, and 19 were positive for staphylococci. On September 19, the child was operated upon. Examination of the patient on the operating table showed a large diffuse fluctuant mass over the second, third, and fourth lumbar vertebrae. A longitudinal incision about 4 inches in length was made over the spinous processes; this revealed the mass to be a large abscess which extended below the muscle layer above and below. A culture was taken of the pus which escaped. The report named gram-positive cocci, morphologically identical with staphylococococcus. About eight ounces of thick purulent pus were evacuated. The spinous processes were then exposed, and the spine of the second lumbar vertebra was visible, denuded of periosteum. There was osteomyelitis of the second lumbar vertebra. The spinous process was removed and the laminae opened; free pus escaped. The spinal canal in the region of the second lumbar vertebra was then explored. The dura was found to be inflamed and partially destroyed in this region. No free pus escaped from the subdural space. The wound was packed with vaseline gauze. Patient left the operating table in excellent condition.

On September 20, the blood culture was negative for the first time, and the bacteriophage was stopped. The following day the temperature did not go above 99.6° F. The child showed definite improvement. The operative wound discharged a large amount of seropurulent pus around the vaseline gauze pack for several days. By September 29, the hemoglobin had fallen to 46 per cent, and she was given a second transfusion of 320 c.c. of whole blood. The wound continued to discharge and was slow in granulating. It was repacked with vaseline gauze. The child's general condition continued to improve slowly. October 19, one month after operation and drainage, a cisternal puncture showed three cells, no globulin, 73 mg. of sugar, and the smear and culture were both negative. By October 25, the back wound had ceased discharging and was granulating. The abscess on the left wrist was incised, and about 1 dram of pus removed. The culture was morphologically identical with staphylococcus. By November 2, the back wound was practically healed, and on November 8, the child was discharged to the convalescent home at Farmington.

Feb. 6, 1932, a sequestrum was removed from the back wound, but physical examination at this time (Mar. 28, 1932) shows all wounds to be completely healed. There are no paralyses. There is no limitation of motion in the spine, and the child walks normally.

SUMMARY

1. An unusual complication of a staphylococcus septicemia is presented.

2. The case demonstrates the value of open operation in the treatment of perimeningitis.

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749 DAVID WHITNEY BUILDING

PULMONARY LESIONS RESEMBLING PNEUMONIA AS THE RESULT OF ALLERGIC SHOCK

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IN ANIMALS which survive anaphylactic shock following an injection of antigen, the syndrome of protracted shock occasionally develops. Zinsser[1] describes the following as its manifestations: dyspnea, irregularity of breathing, partial pulmonary emphysema, and fall of blood pressure, drop in temperature which is followed by a moderate degree of fever. Dean and Webb[2] state that in the more severe cases of anaphylactic shock in dogs which did not terminate fatally, another train of symptoms occurred after the acute state had subsided: dyspnea, fever, diarrhea, stupor, vomiting, and general malaise. In guinea pigs, Ratner and his coworkers[3] produced a similar if not an identical condition by means of continued exposure to the antigenic substance after the production of shock. It is possible that Ishioka,[4] Busson,[5] Friedberger,[6] and Fried[7] refer to the same syndrome when they speak of "sterile anaphylactic pneumonia." They produced this condition in guinea pigs sensitized to horse serum upon insufflation of horse serum into the trachea. The lesions which thus arise under properly controlled conditions may either offer the picture of interstitial bronchopneumonia, or they may involve whole lobes. The authors noticed in the lungs hemorrhagic infarctions of various sizes associated with inflammatory lesions. The mode of production of these lesions, their aseptic character in the early stage, the presence of lymphocytes suggested to them a pathologic differentiation from true pneumonia.

One of us has recently[8] reported cases of severe allergic shock following injection of extracts of cottonseed and horse hair. In two cases eight and twenty hours, respectively, after the injection and after the subsidence of the primary symptoms, slight fever, râles in the lungs, and areas of impaired percussion developed. The clinical picture of a low grade bronchopneumonia ensued which lasted for three to four days.

A similar occurrence was encountered following the ingestion of an aspirin tablet in a patient with severe asthma. In this case evidence of pulmonary edema developed about eight hours before the pulmonary infection arose. The pneumonic process lasted for four days; the highest temperature was 102° F.

During the course of studies on so-called "thymic death," one of us presented clinical and pathologic evidence that many, if not all, cases thus diagnosed are identical with allergic shock. In a large percentage

of these patients after there had been a sudden collapse, dyspnea, and wheezing, the clinical picture of an atypical pneumonia developed. The following is a typical case:

CASE 1.—S. L., one year old, male, had been in perfect health except for frequent nasal catarrhs (allergic?). No family history was obtainable because the child was a foundling. About one week before death he had an afebrile upper respiratory catarrh from which he recovered in several days. On the morning of the day of death he seemed playful and in good health, the temperature being normal. At 10 A.M., while drinking a glass of milk, he suddenly became cyanotic, dyspneic, and vomited. The cyanosis and dyspnea increased, moist râles were noted in the lungs, and signs of consolidation developed. At noon the temperature was 102° F. by rectum; at 3 P.M. the temperature had risen to 103° F., and at 6 P.M. the child expired. The postmortem examination (Dr. L. Parker, at Kalamazoo, Mich.) showed throughout both lungs, dilatation of capillaries, exudation of fluid into the alveoli and extravasation of blood cells, areas of emphysema alternating with atelectasis. Some of these lesions showed leucocytic infiltration as seen in early pneumonia. There was some congestion of the spleen and kidneys, the adrenals were not examined. There was a hyperplasia of the bronchial and mediastinal lymph glands and of the thymus (40 gm.). Other organs, particularly the heart, were found normal.

In this as well as in the other cases studied, the microscopic appearance of the lungs suggested that there was a primary edema of the lungs associated with atelectatic and emphysematous areas upon which the infectious process seemed to be superimposed. This was particularly noticeable in some of the slides in which the leucocytic infiltration involved only the marginal parts of the edematous lesions. Such causes as asphyxial death by food lodged in the trachea, infection of atelectatic areas of the lungs, or primary bronchiolitis could definitely be ruled out by the autopsy findings.

Considering this evidence for the explanation of this type of pulmonary infection, we thought that it would be of value to establish certain clinical features which will lead to a proper recognition, evaluation, and therapy of this condition. Such an attempt was made by studying the records of twelve asthmatic children who had been admitted to the Children's Hospital of Michigan on account of pneumonia. In five, the onset and clinical course did not differ from the usual type of pneumonia. There were chills, high temperature, marked prostration, and the usual physical signs of pneumonia. In seven cases, however, there was an afebrile period ranging from six hours to five days, which was characterized by wheezing and dyspnea and by collapse. During this stage there were crepitant râles in the chest, and in two cases blood-streaked sputum was expectorated. The average leucocyte count was 16,600; the average highest temperature, 102.3° F.; the average duration of the febrile period, four days. On the whole the disease was much milder than bronchopneumonia. The x-ray examinations revealed a generalized mottling of the lungs, particularly of the lower areas. Toward the end of the febrile period there was either a slight residue of a bronchopneumonic process and prominence of the hilum shadow, or the picture was entirely negative. The following are two typical instances

which are of particular interest because the patients had been seen by us shortly before and during the development of this condition.

CASE 2.—F. H., a one-year-old girl, with a family history of allergy had been under our care for the preceding four months on account of asthmatic attacks. She had been found sensitive to various substances, showing particularly strong reactions to orris root, cattle hair, and apples. The asthmatic seizures always appeared to be very severe and on several occasions were followed by fever.

On Apr. 4, 1934, she was seen in the afternoon in a severe attack of asthma, showing evidence of collapse. The temperature then was 97° F. The chest showed asthmatic rhonchi, some hyperresonance throughout, and no impairment of the percussion note. Epinephrine in doses of 1/10 to 2/10 c.c. was given repeatedly without effect. Three hours later the child had to be admitted to the hospital, extremely cyanotic and in a state of shock. The temperature was 102° F., the pulse, 140; the respirations, about 60. In contrast to the lung findings a few hours before, there were fine râles in both lower lobes anteriorly and posteriorly, as well as some asthmatic bruits. There was a general hyperresonance throughout; no areas of dullness could be made out. After rising to 103° F., the temperature dropped on the following day and remained about 100° F. for four days. During this time the asthmatic bruits were heard, but considerably less than before. A marked improvement in the condition set in with the drop of temperature. The white blood count taken on the day after admission was 8,600, the following day, 9,500. The cough had been dry and nonproductive at first and became looser following the second day. An x-ray picture of the chest taken on the third day revealed a slight increase in the hilum markings, but no consolidation.*

This case resembled in appearance those following injections of an overdose of antigen or ingestion of a drug to which sensitivity exists. The extreme degree of shock and the sudden recovery on the following day was particularly dramatic in this case. It is likely, but could not be definitely determined, that some food to which the child was sensitive, had caused the shock. This is suggested by the fact that similar attacks of lesser severity had occurred previously following the ingestion of food to which the child reacted on skin test.

CASE 2.—A. K., an eleven-year-old boy, had been under our care on account of asthma, which was present since infancy. He was found sensitive to various foods and pollen, particularly to tomatoes and short and long ragweed. On Dec. 18, 1933, he was seen in the out-patient department during a severe attack of asthma. The following morning a slight fever, which was said to have ranged between 99° and 102° F., developed. He was admitted to the hospital on the third day of the illness in a state of collapse. There was some cyanosis. A dry nonproductive cough was present. Crepitant and subcrepitant râles were heard over the base of both lungs, more marked on the right side. There were considerably fewer asthmatic rhonchi than on examination three days before. A roentgenogram of the chest showed a process approaching consolidation opposite the right lung root. There was also a definite peritruncal infiltration in the right lower lobe suggesting an "acute process." On admission, the third day following the onset of fever, the white blood count was 8,600; five days later, 15,800. After the child had been in the hospital three days, the temperature became septic in type, varying between 98° and 104° F. daily, for another week. During this latter period no asthma was present. Râles were heard in various portions of the lungs.

*At the beginning of the ragweed season, the child developed hay fever, followed by shock, pulmonary edema and fever, and died within three days. At autopsy the thymus weighed 35 gm.; the lungs showed edematous hemorrhagic lesions with beginning pneumonic patches.

Outside of the fact that wheezing inaugurated this illness, it is interesting to note the relatively low blood count during the first part of the illness, after fever had already been existent for three days.

The characteristic feature in these cases is the development of a low-grade pulmonary infection following an afebrile period with severe asthma and the evidence of pulmonary edema which was associated with shock. While there cannot be any doubt as to the secondary character of this pulmonary process, it is difficult to ascertain from the clinical evidence alone whether we are dealing with a primary allergic edema of the lungs or whether the infection is due to localized atelectasis resulting from plugging off of smaller bronchi by mucus. However, the evidence which one of us has presented (Waldbott[9]) elsewhere on the pathology of allergic shock points to the former explanation. This conception is further strengthened by the following observations:

1. Urticaria in the lungs. Cole and Korns[10] recently described a case of generalized urticaria in which the edema appeared to have spread down through the mucosa of the bronchi into the lungs. The patient finally succumbed to pneumonia.

2. Analogy with allergic processes in other organs. There is a growing belief that the allergic wheal may involve any organ of the system. It has been brought out by Kline and Young[11] that inflammation of such lesions is not uncommon. The best known instance of such a development is the occurrence of nasal and paranasal infections following hay fever and other types of vasomotor rhinitis. One of us (Waldbott[12]) has made similar observations on the trachea and the upper bronchial tree by describing the clinical syndrome of allergic bronchitis. Young and Kline showed that an analogous process may occur in the appendix as well as in other parts of the gastrointestinal tract.

3. Sudden death in asthma with pneumonia. MacDermid[13] described the case of an asthmatic individual in whom an injection of horse serum was followed by pneumonia. At autopsy hemorrhagic areas were present throughout the lungs associated with bronchopneumonia. He concluded that these lesions were the result of allergic shock. His microscopic sections, which we had the privilege to examine, illustrate more than any other autopsy material on record how infectious processes may arise from hemorrhagic edematous areas due to shock.

In his papers on the pulmonary lesions of shock Moon[14] pointed out that a similar edema in the lungs may occur following such conditions as toxemia of pregnancy, infectious disease, burns, and intestinal obstruction. For the explanation of the edema which was not secondary to any cardiac or kidney changes, he referred to the work of Dale, Laidlow, and Richards on histamine shock and considered its origin as being due to a histaminelike substance. Whether he is dealing with an allergic phenomenon and whether the condition which he described is identical with the lung findings in allergic shock is difficult to say. There may possibly be a relationship between the lesions under consideration here

and those described by Moon, similar to that which exists in the allergic wheal and the histamine wheal. Whatever the explanation may be, it is reasonable to assume that edematous lesions of this type are subject to inflammatory changes.

To the clinician, the above observations are of definite importance, both in diagnostic and therapeutic regard. First, this indicates that a history of pneumonia or "influenza" in an allergic child may be the result of an allergic pulmonary reaction, rather than that of a primary infection. Therefore a residue of this disease or an aggravation of the allergic state by the so-called "pneumonia" should not be considered as an indication that this patient's asthma is of an infectious type. Second, in treating such "pneumonia," repeated small doses of epinephrine to combat the edema, removal of sensitizing agents, and measures usually advocated for combating edema, may be of paramount importance and may possibly constitute a life-saving procedure. That contact with sensitizing agents greatly aggravates this condition has been reported elsewhere (Waldbott[8]).

CONCLUSION

1. In allergic patients, pulmonary infections resembling bronchopneumonia may arise as the result of allergic shock and of severe asthma.

2. Evidence is presented which suggests that these lesions are superimposed upon an edematous hemorrhagic process of allergic origin in the lungs.

3. In seven out of twelve asthmatic children who had been hospitalized on account of pneumonia, the infectious process may have thus been originated.

4. In an attempt to differentiate this type of pneumonia from other pulmonary lesions, the following clinical features were found to be of diagnostic value: the presence of an afebrile period with collapse and associated asthmatic symptoms, a lesser severity of the infection and a shorter duration than in the ordinary pneumonia, and a relatively low white blood count at the onset of the febrile period.

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ROENTGENOLOGIC STUDIES OF THE INFANT'S GASTROINTESTINAL TRACT

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INTRODUCTION

ROENTGENOLOGIC studies of the infant's gastrointestinal tract have been made by several investigators. The early work on this subject was carried out by Leven and Barrett[1] in Paris (quoted by Carman),[2] and by Ladd,[3] and Pisek and Le Wald[4] in this country. Since that time there have been several publications on similar studies. On reviewing this literature, we were impressed with the diversity of opinions concerning the size, shape, and emptying time of the stomach. Several of these studies were carried on under special conditions, which may account for some of the variations in the results. We believed that a routine study of the infant gastrointestinal tract would be of value since, in practical radiology, routine rather than special methods are most often used. It is then the purpose of this study to attempt to define the variations which may be found in the gastrointestinal tracts of average healthy infants as seen under routine conditions.

MATERIAL AND TECHNIC

Our studies have been made over a period of four years at the Florence Crittenton Home, Denver. Roentgen ray gastrointestinal examinations were made on 133 infants (63 boys and 70 girls), aged from one week to six months. Each infant was given a barium meal, and 100 of this same group, a barium enema. On some of the infants, several examinations were made at different ages. The age periods varied somewhat, but an attempt was made to obtain the first examinations during the second week of life; the second, third, and fourth series at one month, three months, and six months, respectively. The barium enema was given only during the first ten days of life.

In this group there were included those who were healthy and normal according to history and careful clinical examination and forty-one abnormal infants. In the abnormal groups there were eleven

From the Child Research Council and the University of Colorado School of Medicine.

Thanks are due to Jennie Pings, R. N., and the staff of the Florence Crittenton Home.

TABLE I

THE NUMBER OF EXAMINATIONS PER INFANT

Infants with one examination	43
Infants with two examinations	38
Infants with three examinations	46
Infants with four examinations	6
Total number of infants	133
Total number of examinations	281

babies from syphilitic mothers, nine infants with eczema, five premature infants with birth weights from 2.0 kg. to 2.2 kg., and sixteen infants showing minor disturbances, such as upper respiratory infections, mild diarrhea, mild constipation, and questionable hypertonicity. As a careful examination and comparison of the roentgenograms failed to show any distinguishing features, the normal and abnormal cases are all considered together as representing a group of average nursery babies.

The barium meal consisted of 5 c.c. of a 2 per cent gum arabic solution mixed with 8 gm. of barium and added to each ounce of the infant's usual formula. (The majority of the group were on whole milk, water and dextri-maltose mixtures, averaging approximately 45 calories per pound.) The meal was bottle fed. Immediately after completion of the feeding, the infant was rotated on the right side and the first x-ray exposure was made with the rays passing through the left post-axillary line (Fig. 4). This position was used in an effort to portray the pylorus and duodenum better. The progress of the meal through the gastrointestinal tract was then followed by posterior-anterior films made at one and one-half hours, three hours, five hours, eight hours, and twenty-four hours after completion of the meal. The infants were placed in no special position during the process of digestion of the meal. In the series of the 133 infants the regular feedings were continued at four-hour intervals. In a special series of ten infants nothing was given by mouth until the stomach was empty.

The barium enema consisted of 5 c.c. of 2 per cent gum arabic solution and 8 gm. of barium for each ounce of water. About 30 c.c. was given through a small catheter. Following the enema a film was made in the posterior-anterior position.

The gum arabic solution was added to the barium mixture for both the meal and enema, as it was found, in our experience, to give better suspension of the barium and a better filling of the stomach and intestine. When barium alone was given without the gum arabic solution, the meal tended to precipitate out and form a small ball in the stomach and intestine and gave poor visualization. Furthermore, the gum arabic barium meal does not tend to constipate the infant as much as is sometimes noted the barium alone does.

OBSERVATIONS OF THE BARIUM MEAL

1. *Esophagus.*—No attempt was made to visualize the esophagus. It was, however, seen seven times in the 281 examinations on the film made immediately after completion of the barium meal. It did not continue to show on subsequent examinations, nor was it present on examinations made on the same infant at different age periods.

2. *Stomach.*—a. Shape: The infant stomach does not tend to assume fairly definite types or forms as does the so-called "adult type" of stomach. In our series we are unable to classify infant stomachs into

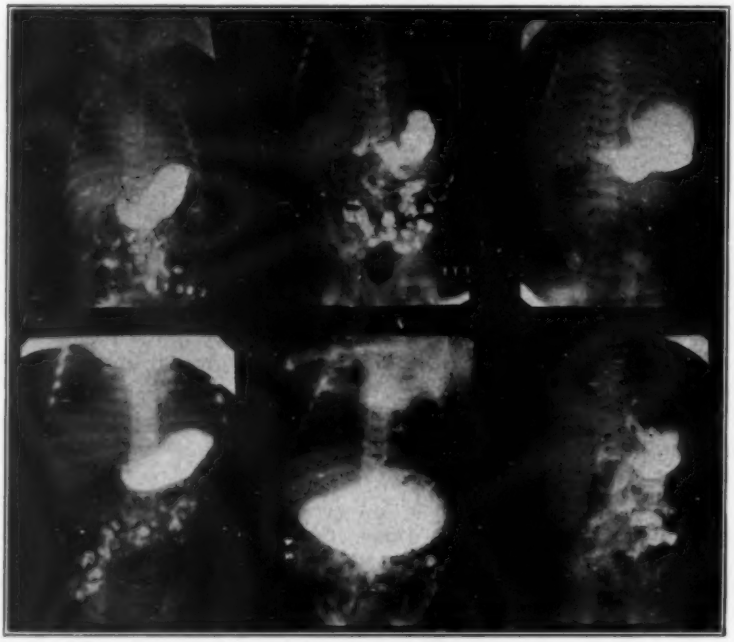

Fig. 1. Roentgenograms of stomachs of six infants from 3 weeks to 4 months old, showing different sizes and shapes.

definite types. They appear to assume many shapes from "pear shape," "oval shape," "retort shape," "tobacco pouch shape," to intermediate shapes which we were unable to classify. The stomach may change from one type to another or may assume several different shapes during the process of emptying and at different ages in the same infant. In the series we found five stomachs which appeared as "steer horn" type and one stomach which appeared as "fishhook" type. Even in these cases the stomach assumed different shapes during the process of emptying and also at subsequent examinations (Fig. 1).

b. *Size:* The size of the stomach is difficult to estimate. It appears to vary greatly during the process of emptying and at subsequent examinations made on the same infant at different age periods. Usually it extends from the dome of the left half of the diaphragm to just beyond the midline of the spine. However, it may appear greatly enlarged if there is a large accumulation of gas; and in several cases it appeared to extend across the entire abdomen (Fig. 1).

c. *Position of the Stomach:* The infant stomach varies from the horizontal to the oblique and almost vertical position. From our series we found the horizontal position to be far more frequent. The position from the horizontal to the oblique may change in different examinations on the same infant, and also during the period of emptying of the stomach.

TABLE II

POSITION OF THE STOMACH AFTER BARIUM MEAL

Horizontal	265
Vertical	3
Oblique	13
Total examinations	281

Any classification into horizontal, oblique, or vertical positions is more or less arbitrary, as there is a great variation in the different angles, and at times it is difficult to determine whether it should be called horizontal or oblique.

d. *Height of the Lower Pole:* The height of the lower pole varied from the top of the first lumbar vertebra to the middle of the third lumbar vertebra as shown on the film taken immediately after the barium meal. It was noted that the height may vary at different examinations of the same infant from one to one and one-half vertebrae, and also during the process of emptying.

e. *Peristalsis:* Peristaltic waves were rarely seen in our series. In the series of 133 infants, only five examinations showed peristalsis, two on the immediate films and three on the one-and-one-half-hour films. In the special series of ten infants, in whom nothing was given by mouth following the barium meal until the stomach was empty, films were made at two minutes, 5 minutes and 10 minutes after the meal was begun, and then every half-hour until the stomach was empty. A total of 137 films were made on these ten infants and even with the comparatively short time intervals between each film peristalsis was rarely seen.

f. *Air Bubble:* It has been observed by Dr. W. W. Wasson and others that soon after the first inspiration of the newborn infant air can be demonstrated in the stomach by x-ray pictures. This air bubble changes size and shape during different examinations and during the process of emptying. Though no definite conclusions can be drawn, it appears to exert no influence upon the emptying time of the stomach.

It is situated in the cardia of the stomach and in some cases appears to increase in size as the stomach empties.

g. *Emptying Time:* The films taken immediately after completion of the barium meal showed the presence of the meal in the small intestine in 244 out of 281 examinations. This would seem to indicate that the stomach begins to empty very soon after the meal is given. This was borne out by fluoroscopic examination of three cases and in the special series of ten cases, which showed small masses in the small intestine in from five to ten minutes after the beginning of the meal. The emptying time of the regular series of 133 infants as checked by films taken one and one-half hours, three hours, five hours, and eight hours after the completion of the barium meal is shown in Table III.

TABLE III

VARIATION IN THE EMPTYING TIME OF THE STOMACH

	NO.	PERCENTAGE
Emptying time at one and one-half hours	5	2
Emptying time from 1½ to 3 hours	27	9
Emptying time 3 to 5 hours	56	19
Emptying time 5 to 8 hours	80	27
Emptying time more than 8 hours	123	43
Totals	281	100

NOTE: The true emptying time may be obscure as the estimation of the amount of barium residue appearing on the film is quite difficult. The residue in some cases appeared to be a large amount, while in others it was only a small amount. When the stomach showed only a few flakes, apparently adherent to the gastric mucosa, it was considered as empty. (See Fig. 4, series 2.)

In some cases there appeared to be rapid emptying during the first few hours, then somewhat slower emptying. In several cases in which the small intestines were apparently empty in from five to eight hours, the colon was fairly well filled, and there appeared a gastric residue. The emptying time of the stomach does not tend to be the same at different examinations of the same infant. An example of this is shown in one of the infants whose stomach emptied in one and one-half hours at one examination, in five to eight hours, and in more than eight hours on the second and third examinations. It must be noted that the above data applies to those cases which were given the regular formula four hours after the barium meal. The ten special cases in which no food was given following the barium meal until the stomach was empty showed a slightly different time of emptying. Five of the ten infants showed an emptying time of from three to five hours, and five infants, from five to eight hours. None of these showed a residue at the end of eight hours. If we may be allowed to draw conclusions from this small group, it would appear that feeding the infant within the four-hour period, or before the stomach was empty, did tend to lengthen the emptying time.

h. *Pylorus:* The pylorus was seen on the immediate film in only eleven instances out of 281 examinations. It was more frequently seen on the one-and-one-half-hour films (fifty-eight times) and on the three-hour films (thirty-two times). It does not appear to be as well marked in the infant as in the adult (Fig. 2). In the special series of ten cases, with the films made at frequent intervals, it was not seen until about one and one-half hours and then infrequently. Three infants were given the meal and its progress was watched under the fluoroscope. The stomach was palpated to fill the duodenum. In these cases it was noted that the pylorus was not well defined.

3. *Small Intestine.*—As the stomach began to empty, the small intestine became visualized by small separated irregular masses of barium. In the special series of cases these barium masses appeared between five and twelve minutes after the beginning of feeding (Fig. 2). In the general series they were seen in 244 out of 281 examinations on the immediate film, made after the completion of the feeding.

a. *Duodenum:* The duodenum was rarely seen on the film made immediately after completion of the barium meal (9 times in 281 examinations). On the one-and-one-half-hour and three-hour films, it was seen twenty times and three times, respectively. A study of the observations under the fluoroscope of the three infants and the special series of 10 cases showed the pylorus and the duodenum to be seen most often from one to three hours after the barium meal. When the duodenum was seen, it differed from the adult appearance. The typical cap was seen only once. Usually it appeared as an annular structure, all portions being approximately of the same size, and curving downward and to the left (Fig. 2).

b. *Jejunum:* The jejunum was rarely visualized with barium, and, when it was seen, it did not present the "feathery" appearance of the "adult" type. Instead, it appeared sometimes as small isolated masses of barium and other times as a thin continuous line of barium. Occasionally these separated globules were fuzzy in appearance in contrast to the clearly cut masses in the lower part of the small intestine (Figs. 2 and 4). The progress of the meal from the pylorus through the duodenum and jejunum was rarely seen in our films.

c. *Ileum:* Small globules of barium were frequently seen in the ileum on the immediate and subsequent films as late as five hours. These globules may arrange themselves to show many patterns; as more or less isolated from each other, grouped in several bunches, or even grouped in masses in the lower right or left quadrant (Figs. 2 and 4).

4. *Large Intestine.*—a. *Cecum:* On the three-hour film globules of barium were frequently grouped near the ileocecal junction, and the cecum often showed partial filling. At five hours it was usually well filled, and at eight hours there were still a large number of examina-

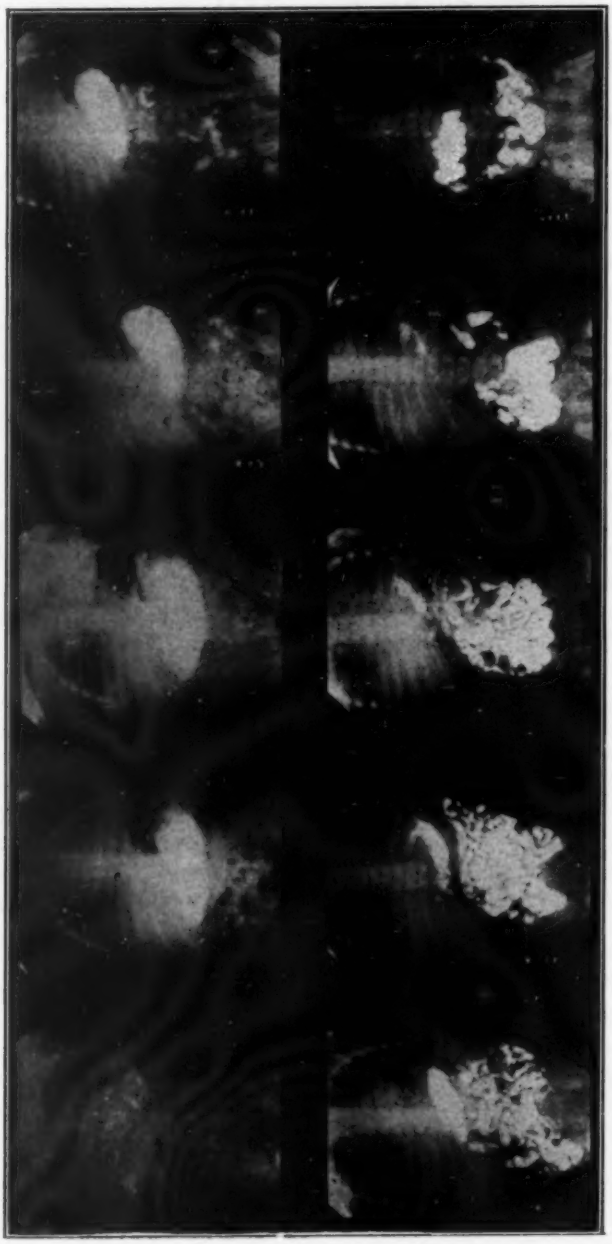

Fig. 2.—Reproduction of gastrointestinal series in one of the ten special cases. Films taken at 4 minutes, 7 minutes, 12 minutes, 1 hr., 1½ hrs., 3 hrs., 3½ hrs., 4 hrs., 4½ hrs., and 6 hrs., after the beginning of feeding.

tions which showed the cecum to be well filled. At twenty-four hours there were only two out of 281 examinations which showed the cecum filled and the rest of the colon empty.

b. *Appendix:* The appendix was visualized in only two instances out of 281 examinations. Both visualizations belonged to cases which failed to show the appendix on subsequent examinations.

c. *Colon:* Following the barium meal the colon was empty in 9 out of 281 examinations at eight hours. At twenty-four hours the amount of filling is shown in Table IV.

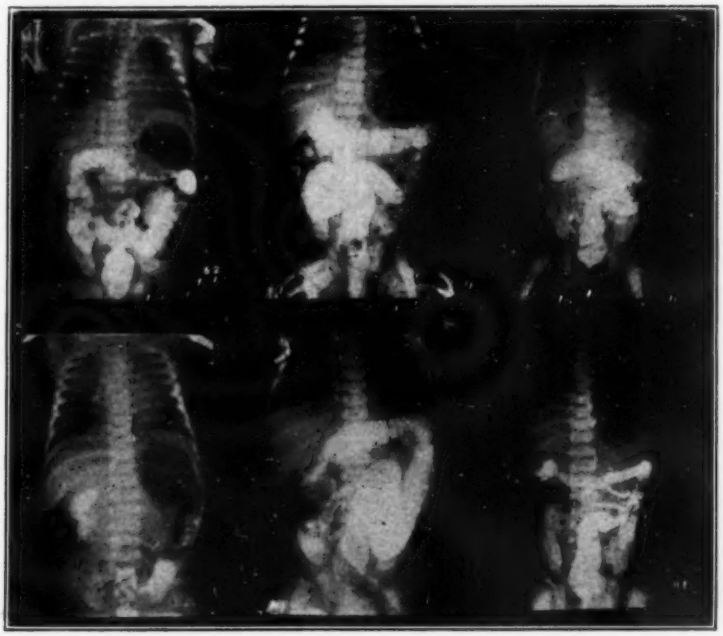

Fig. 3.—Roentgenograms of colons after barium enema.

TABLE IV

AMOUNT OF FILLING OF THE COLON TWENTY-FOUR HOURS AFTER BARIUM MEAL

Colon—entire colon filled	24
Sigmoid to hepatic flexure	4
Sigmoid to splenic flexure	17
Sigmoid colon alone	64
Cecum alone filled	2
Colon entirely empty	170
Total examinations	281

In those twenty-four examinations in which the entire colon was filled and in the four cases in which it was filled from the sigmoid to

the hepatic flexure following the barium meal, it was noted that the haustrations were more marked than shown on the same cases following a barium enema. As there were so few colons filled following the barium meal, a detailed study of the colon was made after the barium enema. The results of the barium enema for a routine study were disappointing. It was found that the infant retained the barium better if no cleansing enema had been given prior to the giving of a barium enema. Even when this technic was followed, the colon in a number of instances did not retain sufficient barium for a long enough interval to allow the making of a satisfactory x-ray exposure (Table V).

TABLE V

AMOUNT OF FILLING OF THE COLON AS SHOWN ON THE ROENTGENOGRAM AFTER BARIUM ENEMA

Not filled	41
Filled to the sigmoid	16
Filled to the splenic flexure	7
Filled to hepatic flexure	18
Filled to cecum	18
Total cases	100

d. *Redundancy of the Sigmoid:* All of the barium enemas were studied for the degree of redundancy of the sigmoid (Fig. 3). Even in those cases in which there was no filling of the colon, the amount of gas present and the few flakes of barium remaining usually showed the location and course of the sigmoid.

TABLE VI

REDUNDANCY OF THE SIGMOID

Barium enema films not readable	19
Mild redundancy	2
Moderate redundancy	13
Marked redundancy	62
Very marked redundancy	4
Total cases	100

Apparently there was no correlation between the redundancy of the sigmoid and the emptying time of the colon. In the four cases which showed the most marked redundancy and the two cases which showed no redundancy, the emptying time of the colon varied greatly as shown by Table VII.

In cases showing moderate and marked redundancy, the correlation seemed equally impossible as the emptying time of the colon varied in different individuals of the same age and on different examinations of the same individual over a period of months.

e. *Spasm of the Colon:* Thirty-six cases which showed sufficient barium filling of the colon after the barium enema were examined as to the amount of spasm shown on the films (Fig. 3). The results showed no spasm in 20 cases and spasm in 16 cases. The location of the spasm varied in the different cases. As only one barium enema

TABLE VII

CASE NO.	TWENTY-FOUR-HOUR FILM	FINDING
	Cases Showing Very Marked Redundancy	
77	1st Examination	Entire colon filled
	2nd Examination	Colon empty
	3rd Examination	Colon empty
82	1st Examination	Colon empty
	2nd Examination	Sigmoid colon filled
	3rd Examination	Sigmoid colon filled
85	1st Examination	Sigmoid colon filled
	2nd Examination	Sigmoid colon filled
	3rd Examination	Colon empty
125	1st Examination	Colon empty
	2nd Examination	Colon empty
	Cases Showing No Redundancy	
57	1st Examination	Sigmoid filled
	2nd Examination	Entire colon filled
127	1st Examination	Colon empty
	2nd Examination	Colon empty
	3rd Examination	Sigmoid filled

was given to each infant, the location of the spasm was not determined on different examinations of the same infant. Well-filled colons after the barium meal rarely showed spasm although after the barium enema these infants sometimes showed spasm. With the barium enema, six infants showed spasm in more than one portion of the colon. There was no significant correlation between the degree of spasm shown in the colon following barium enema and the speed of emptying of the same colons following the barium meal.

f. *Haustrations:* Twenty-eight infants given barium enema could be examined for the presence of haustrations. No haustrations were found in 16 cases, and haustrations were found in 12 cases. The position and degree of haustrations appeared to vary greatly. They are not as marked as in the adult type of colon. In the same cases the colon as seen on the eight-hour and twenty-four-hour film following barium meal usually showed more haustrations than on the barium enema film.

g. *Flexures:* There were thirty-one infants in whom the flexures could be studied. Nine of these showed annular or very poorly marked flexures, and twenty-two showed angulated flexures (Fig. 3).

ABNORMAL CASES

Premature Infants.—There were five premature infants with birth weights from 2.0 kg. to 2.2 kg., on whom fourteen examinations were made. There was no marked decrease in the emptying time of the stomach. Of the fourteen examinations made eight showed emptying at five hours, thus showing a larger percentage empty in five hours than that shown by the group as a whole. No other differences were noted. However, this series is too small to draw any conclusions.

Eczema.—There were nine cases of eczema. The examinations showed no significant changes as compared with the normal group.

Syphilis.—The eleven infants from syphilitic mothers also showed no marked changes in the gastrointestinal roentgenograms.

Minor Disturbances.—Sixteen infants comprising those showing minor clinical disturbances, such as slight constipation, upper respiratory infections, mild diarrhea, and questionable hypertonicity, were not found to differ from the rest of the series in the roentgenologic studies.

DISCUSSION

According to the literature, there is great variance in the observations and conclusions in regard to the gastrointestinal tract of infants. We should like to compare some of our findings with those of earlier workers.

There has been a great deal of difference of opinion as to stomach form. Alwens and Husler[5] described three types of stomach dependent on the taking of fluids in the vertical position, the taking of fluids in the horizontal position, or the taking of gruels of thick consistency in the vertical position. The basis of this classification is the air bubble.

Theile[6] describe two main types of stomach, the "bagpipe" form of Leven and Barrett and the "tobacco pouch" form of Pisek and Le Wald. However, he states there may be infinite varieties of transitional forms. Pisek and Le Wald stated that there is no definite form of stomach in the infant.

Finally Rogatz[7] using no contrast medium divided the infant stomach into two main types: (1) the shape of a pear or flask lying on its side with a large, circular fundus and a smaller narrow pyloric area; (2) smooth elliptical or oval in shape, occurring less frequently. He also describes a third form, common to both when thick gruels are ingested, namely, a small circular or oval form about one-third the size of the fluid forms with little or no air bubble at all.

From our observations we are forced to the conclusions, in agreement with Pisek and Le Wald, that there is no constant form of the infant stomach in the roentgenogram and that there are wide variations in different individuals and even in the same individual at various times. In agreement with Pisek and Le Wald, Leven and Barrett, Flesch and Peteri,[8] Trumpp,[9] and Rogatz,[7] we found that the long axis of the stomach is almost always horizontal.

In agreement with Ladd and other workers we rarely found peristalsis in the stomach. Rogatz[10] described a definite "peristolic function," that is the capacity of the stomach wall to surround or grasp its contents following the ingestion of food. This is not to be confused with the more familiar peristaltic function.

The emptying time of the infant's stomach has been studied by various workers and the times given vary greatly. (See Table VIII.)

We have found in normal infants some barium may be visualized in the stomach even after 8 hours. Ladd states that if a feeding is given after the barium meal, there is a tendency to faster emptying. We

TABLE VIII

EMPTYING TIME OF STOMACH

	TIME WITH BREAST FEEDING	TIME WITH ARTIFICIAL FEEDING	AUTHOR
Newborns	2 -3 hr.	3 -4 hr.	Vogt[11]
Nurslings	3 hr.	5 hr.	Alwens[5]
	2½ hr.	2½-8 hr.	Ladd[3]
	3 hr.	4 hr.	Kerley[12]
	2 -3 hr.	3 -4 hr.	Theile[6]
	1½-2 hr.	3 -5 hr.	Kahn[13]
	1½-4 hr.	2½-4 hr.	Bessau[14]
		1 hr. 40 min.-over 3 hr. 40 min.	Shukry[15]
	3 -4 hr.		Izumita[16]
	Av. 3½-4⅔ hr.		
		3⅓-6⅔ hr.	Demuth[17]

were not able to confirm this. In our regular series the infants were fed again their regular formula four hours after the barium meal, and it will be noted (Table III) that as high as 43 per cent of these children showed some residue after eight hours. In the ten special cases in which no feeding or water was given after the barium meal until the stomach was empty, our longest emptying time was between six and one-half and seven hours.

De Buys and Henriques[18] state that motility of the stomach is more rapid when the child is placed in the right lateral position, and comparatively slow in the supine position. In our series the child was usually in the supine position though no attempt was made to have the child in any fixed position.

In agreement with other observers we found that the meal finds its way into the small intestines very quickly after the beginning of feeding. Le Wald[19] states that the duodenum rarely shows the caplike appearance in infants. We found that this was the case and also that the pylorus and duodenum were difficult to visualize. From our observations the infant jejunum does not present the adult feathery appearance. We have not found this previously mentioned in the literature, and we have no explanation for it. The emptying time of the small intestine in children has been studied by Kahn[20] who gives the time in stomach as four to five hours, small intestines, as seven to eight hours, large intestines, as two to fourteen hours. With dye stuff the entire passage took from four to twenty hours, on the average about fifteen hours. De Backer and van de Putte[21] found that the small intestinal tract is not emptied until after eight hours; after two and one-half hours the contrast meal may be in the cecum, in six to seven hours to the splenic flexure, and in eight hours in the sigmoid flexure, and the entire intestinal tract is free in from eighteen to twenty-four hours.

In our series of 281 examinations the eight-hour film showed nine instances and the twenty-four-hour film, 170 instances in which the entire tract was empty (Table IV). Although there has been a very

Fig. 4.—Roentgenograms after barium meal, illustrating an average infant at three weeks and at six weeks.

adequate anatomic study of the infant colon by Scammon,[22] roentgen studies of the normal colon seem to have been neglected. In a general way our observations bear out the anatomical findings of Scammon: i.e., haustrations were poorly marked; the sigmoid colon appeared relatively long and redundant; and the flexures were not as well marked as in the adult.

RÉSUMÉ OF FINDINGS IN AVERAGE CASE

The progress of the meal may be briefly summarized as follows (compare Fig. 4):

Immediate film

The stomach began to empty. Small globules of barium were seen in the lower part of the small intestine. The pylorus, duodenum, and jejunum were rarely seen. No meal was visualized near the ileocecal junction.

One-and-one-half-hour film

The stomach still showed a considerable quantity of meal. It was empty in five out of 281 examinations. Frequently it had changed its shape from that shown on the immediate film. The pylorus, duodenum, and jejunum were more often seen on this examination than on the immediate film. Globules in the ileum had increased in number and were well disseminated or shown as groupings in various patterns. The meal had not yet reached the ileocecal junction.

Three-hour film

The stomach was empty in thirty-two, 11 per cent, out of 281 examinations. The pylorus, duodenum, and jejunum were not seen as often as on the one-and-one-half-hour film. When there was a gastric residue, it varied considerably as to the amount of meal in different cases and different examinations in the same case. The shape had frequently changed from that shown on the previous films. Globules of barium were frequently grouped near the ileocecal junction, and the cecum often showed partial filling.

Five-hour film

The stomach was empty in eighty-eight, 30 per cent, out of 281 examinations. The pylorus, duodenum, and jejunum were uncommonly seen. Scattered masses were often seen throughout the small intestine, and the colon was usually well filled from the cecum to the middle of the transverse colon, and sometimes to the splenic flexure (twenty-four examinations).

Eight-hour film

The stomach was empty in 168, 47 per cent, examinations out of 281. In the 123, 43 per cent, examinations which showed gastric residue, it usually appeared as a very small amount. The gas bubble was often quite large whether or not the stomach was empty. The small intestine frequently showed small scattered masses of barium. The colon was well filled in ten cases, in the other cases there were isolated masses

of barium. The colon and entire gastrointestinal tract were empty in nine examinations out of 281.

Twenty-four-hour film

The stomach was empty in all examinations. Small intestine rarely showed a few isolated globules of barium. The colon was entirely empty in 170 out of 281 examinations (Table IV).

SUMMARY

1. Two hundred and eighty-one roentgenologic gastrointestinal examinations were made on 133 infants (sixty-three boys and seventy girls), aged from one week to six months.

2. Barium enemas were given to 100 of these infants.

3. The study of the films shows that marked variations may be found between individuals or in any one individual at different times.

4. These are illustrated by such findings as: (1) the variation in the emptying time of the stomach which is from one and one-half to more than eight hours; (2) the lack of any constant shape of the stomach; (3) the changing pattern presented by the globules of barium in the jejunum and ileum; or (4) the variation in the amount of redundancy of the sigmoid.

5. Thirty-four roentgenograms selected from the 1,686 films of these 133 infants have been reproduced to illustrate the individual variations noted.

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Critical Review

NORMAL NUTRITION DURING CHILDHOOD

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PREVIOUS reviews of this series have dealt with problems of nutrition in general and with the feeding of the normal infant. This presentation will offer a review of some concepts pertaining to the nutrition of the child from the period following infancy through adolescence and will have as its thesis the desirability of dietary supervision throughout the whole period. Consideration of therapeutic dietary measures will be reserved for presentation at another time.

In review, the quantitative and qualitative food needs of the body stand in direct relationship to the quantity and quality of growth and expenditure of energy. Defects of nutrition may be masked; absence of outstanding disease offers no evidence that the diet is adequate. Food which satisfies the appetite will not necessarily meet the body's needs; in fact, with the types of foodstuffs customarily employed as the chief constituents of the dietary, the likelihood of qualitative inadequacy of such a regimen is great. Within limits the quantity of growth will be determined by the minimal allowance of any of the dietary essentials; in some instances, gross growth may seem ample, yet with minimal intakes of certain essentials the quality of tissue composition may be deficient. Not only are the amounts of the various essentials important, but also the ratio which one bears to another. Fortunately, in any type of mixed dietary usually employed in the average community, many of the phases of the diet will be met adequately without any special consideration. This holds for most of the minerals used in the body and as well for the calories. Potential defects most common in the diet of the child in this country pertain to the amount and quality of protein ingested, the amount of calcium and phosphorus offered and the ratio in which they exist in the diet, and the allowance of iron, iodine, and the various vitamins. Of the latter, certain diets habitually used may approach inadequacy in numerous regards; probably special consideration is required to insure sufficient intake of vitamins D, A, C, G and B, the need for emphasis decreasing in the order named.

The need for supervision of the diet of the infant has been forced into the consciousness of the medical and lay public within the past two decades and now is quite generally accepted and practiced with varying degrees of thoroughness and insight. From the emphasis placed on the diet of the infant, one might conclude by inference that the nutritional needs of the infant differ in some significant manner from that of the human organism at any later period of life. While the state of infancy does offer certain nutritional problems peculiar to that age of life, the

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qualitative needs of the tissues are probably no different at one period of childhood than at another. The needs during growth are differentiated quantitatively from those of later life by the increased requirements for the substances entering into the composition of the tissues. The child has a lower margin of safety in regard to his nutritive requirements, and deprivation usually will give rise to disturbances of structure or of function which may or may not make themselves clinically apparent. The state designated as "health" covers such a broad range that one's status may vary widely without falling outside of its boundaries, and since one cannot serve as his own experimental control, it is difficult to demonstrate that a level of health may be attainable different from that experienced by the person who is merely passably healthy.

The infant's complete dependence on his environment for his sustenance makes rigorous dietary supervision essential for his well-being. Moreover, at birth the quantitative composition of his tissues varies from that seen in later infancy, and the diet is responsible for the alterations which occur.[1] Even though the maternal diet has been ample in all regards, and the newborn infant starts life with a reserve supply of iron and of the fat-soluble vitamins sufficient to carry him through the first few weeks of postnatal life, he is born calcium-poor, and this must be corrected early if rickets and osteoporosis are to be avoided and normal growth occur.

Once locomotion is acquired, the child liberates himself in some measure from the nutritional limitations of infancy. His food intake is varied in its constituents, and through avoidance of monotony the likelihood of dietary deficiency is lessened in corresponding degree. This has its advantages and its disadvantages. Frequently the fact is overlooked that his body still requires food suitable and sufficient for growth; the child is put at the table with adults and offered food which is far from ideal for the mature organism and infinitely less fitted for the needs of the growing body. The development of defects of growth or of function are explained away on the basis of inherited tendencies, and the correction which would be possible under suitable dietary control is lost.

Various investigators have studied the types and amounts of foods habitually used in representative sections of their countries and have concluded that the type of dietary commonly employed in this country and in the British Isles is such that various inadequacies of some degree seem inevitable.[2] Deficiencies of vitamin D and of calcium are probably most widespread; according to an English authority, many people are on the borderline of vitamin C deficiency. Recent work indicates the prevalence of moderate vitamin A deficit, as gauged by subclinical degrees of impaired dark adaptation. The widespread occurrence of abnormal conditions generally attributed to diet errors, such as constipation and dental caries, may be taken as evidence that the common dietary leaves much to be desired. The concept that a gulf lies between merely passable health and that attainable through diets which approach more optimum levels emphasizes further the desirability for diet control during childhood.

Since disturbances of nutrition may be masked, many errors may be made in evaluating the adequacy of the food ingested and used by the body. The criterion most frequently employed is that of the body weight compared with a table of standards, in which the child's height may or

may not be taken into consideration. Recognition of the inadequacy of such measurements for this purpose fortunately is gaining ground; a child may weigh less than the standard value for his height, yet not be abnormally thin; on the other hand, he may exceed his predicted value and still be malnourished. Attempts have been made to differentiate the desirable weight ratios for children of varied types of habitus through recognition that the size of the skeleton will determine the amount of soft tissues appropriate for an individual child.[3, 4, 5] Through such means, a fairer evaluation of the quantitative aspect of nutrition may be gained. Physical measurements become much more valuable if obtained at successive intervals on the same child and comparisons made as to the rate of gain. However, many factors other than anthropometric measurements must be considered in estimating the adequacy of nutrition in all its aspects. Such measurements may detect the presence of marked under- or overnutrition, but usually will not reveal the perversions of nutrition for which the term "malnutrition" might well be reserved. Some of these manifest themselves in symptoms or signs which are more or less pathognomonic but which often represent the existence of a vicious cycle usually involving nutritional disturbance as an important link. These may reflect themselves in alteration of the turgor of the tissues, color of the skin and mucous membranes, degree of alertness, or in evidences of apathy or irritability, poor posture, restlessness, disturbed sleep, or other signs of chronic fatigue.[6] The demonstration of appreciable degrees of dental decay or the history of habitual constipation usually may be accepted as sufficient evidence that perverted nutrition exists. Laboratory procedures such as roentgenograms of bones, determination of the levels of various constituents of the serum or metabolic balance periods, may reveal evidences of disturbed nutrition which otherwise might be merely suspected or missed.

The results of different nutritional surveys made in various sections of this country may be taken to indicate either the existence of widespread malnutrition[7] or that little nutritional disturbance exists except under unusual circumstances.[8] This discrepancy is dependent in part on the confusion of quantitative undernutrition with the less obvious evidences of malnutrition or perverted nutrition. Evidences of the latter status do not imply conditions incompatible with life or immediately dangerous, but they are significant in their relation to the efficiency and later health of the individual. One finding of significance in these nutritional surveys is that the nutritional status of children seems actually better since the inauguration of relief measures than theretofore, explainable on the basis of the increased attention to efficient feeding which the recent regimen of relief has inaugurated.[8] Data of this type are illuminating, and, if dietary conditions can be maintained at the improved levels of efficiency, the level of health of the community can be expected to rise correspondingly. If relief becomes unavailable and the children are left to the type of dietary the depressed economic situation will enforce on most, the results will be disastrous. The lessened death rate observed in England during the past two centuries is considered by Harris[9] as dependent in part on the gradually improving level of national nutrition. While this may be taken as evidence of greater availability of suitable foods throughout the year, it must be recognized that financial stress, together with unfamiliarity with the types of foods most needed by the body, will tend to lower the nutritional status unless the

services of persons skilled in the science of nutrition are available to assist in the administration of relief measures.

Many conditions other than poverty can contribute to the establishment of malnutrition.[11] Adequate nutrition involves adequacy of ingestion, digestion, absorption, utilization, and excretion. These may be affected through organic or functional disturbances; the former may depend on the presence of infections or on mechanical causes; the latter on overactivity of body or of mind, or on poor diet habits. Poverty exerts its effects more through parental ignorance or shiftlessness than through inability to obtain nutritionally adequate foods; suitable expenditure of the same amount for food with a wiser choice of foodstuffs would lessen greatly the deficiencies of the diets of the poor. The initial reserve of stored nutritional essentials will condition the appearance of nutritional disturbances.[1] Among mechanical factors conditioning malnutrition, poor teeth, very large tonsils, and nasal obstruction should be mentioned.[11] Appetite will be impaired through persistent postnasal discharge. Physical conditions leading to fatigue will lessen voluntary food intake; such conditions include chronic nasal obstruction, poor vision, or difficult locomotion from any cause. Focal infection can contribute through its rôle in producing nasal obstruction, tonsillar enlargement, and postnasal drip, as well as by the effects of the infection per se; such infections seem to have the effect of diminishing the rate of gastroenteric peristalsis, with delayed emptying time of the stomach. The presence of any illness may serve to lessen the appetite and diminish the intake of suitable food. Diseases which are associated with lessened ability for absorption of digested food may induce deficiency diseases even though the intake is ample.[12] The use of therapeutic diets is a source of danger, unless care is employed to make the diets nutritionally complete. Among the functional causes of diet inadequacy, the psychogenic disturbances are most important among the more well-to-do.[13] These difficulties arise from a basic misconception of the simple facts of nutrition. Under this designation several situations may be included, some of which already have been mentioned. First, the adult members may fail to appreciate the qualitative need for certain types of food for themselves or their children and through either carelessness or ignorance permit the child to choose at will from the foods offered at the table, without any conscious attempt to make the foods offered qualitatively suitable. In general, a child may be expected to adopt the least desirable food habits of his adult associates; this plays a large part in conditioning the type of food intake of the individual throughout his lifetime. On the other hand, overzealous application of imperfect knowledge concerning suitable dietaries may lead to food-consciousness of such a degree that eating becomes a burden rather than a routine performance, and the child through rebellion develops into a feeding problem, and malnutrition results even though suitable food is offered. A similar end-result may obtain when the child is permitted to develop poor or irregular habits of eating, sleeping, bowel function, or other necessary physiologic acts.

Many references pertaining to the value of various foods, singly or in combination, have been cited in the foregoing and in previous reviews of this series. The trend of relevant literature has been to substantiate the views presented therein. Numerous reviews have appeared pertaining to human nutrition as a whole.[1, 2, 9, 10, 14] Other studies have dealt with the body's requirement of the various vitamins, minerals, calories

and protein; with the special values offered by various specific foodstuffs; the rôle played by the acid-base nature of the diet ash on nutrition and body function; and the relationship of diet to resistance to infection.

Sherman, in discussing trends in the recent advances in the chemistry of food and nutrition, comments on the relation in structure between amino acids and the organic catalysts, such as thyroxine, glutathione, adrenin, and insulin. The important rôle played by the amino acids in the body's functions and the limited ability of the body to synthesize them renders it necessary that the body receive the various essential amino acids in the food in sufficient amounts. A newly identified amino acid, methionine, is recognized as an essential component of proteins. He implies also that casein may contain still other units as yet unrecognized.[1] Considerable danger of inadequate ingestion of first-class protein foods exists among children;[14] this is noteworthy only when the ingestion of milk is markedly curtailed. Sherman points out that low milk diets incur the likelihood of deficient intake of calcium and that this may not be apparent clinically but may result in bone of deficient calcium content. Moreover, under such a dietary there is often a parallel deficiency of vitamins A and G. The low content of calcium in the infant's bones at the time of birth is an aid to its delivery but increases the hazard of the development of rickets during infancy unless ample amounts of that mineral and of vitamin D are supplied. The average daily per capita consumption of milk in the state of Illinois during the years 1929-1931 was less than two-thirds of a pint;[17] in England it is much less.[18] The English minimal standards of a pint daily up to the age of five years. and a half pint daily from five to ten years are much lower than those recognized in this country;[15] the customary lowered intake of milk, together with lessened sunshine, may account in considerable measure for the high incidence of rickets described by Harris.[2] He states that a recent survey indicated that 88 per cent of five-year-old children in a large group showed evidences of past rickets and that in 1918 11 per cent of the crippling of school children was ascribed to the residual deformities of that disease. In the report of the conference between the Ministry of Health and the Committee on Nutrition of the British Medical Association dealing with the minimal essentials for a complete diet, the value of milk in the diet was stressed especially, because of its content of first-class protein, minerals and vitamins, together with carbohydrate and fat all "in a naturally balanced form."[16]

Less stress is placed on the necessity of special measures to insure sufficient iron intake after the stage of infancy.[1] The infant born at term is safeguarded through the storage in its body of a supply of iron sufficient to meet his needs in some measure for the first few months of life.

Two recent studies relating to the significance of the acid-base potentialities of the diet seem significant in view of the prominence given to these factors in the advertising of various foodstuffs. Bischoff, Sansum, Long, and DeWar[19] determined the effect on the plasma bicarbonate and the serum pH of various foods and acid and basic salts. Even when large amounts of foods with acid ash were given, no significant or prolonged alteration in the plasma bicarbonate, serum pH, or urine acidity could be established. The eating of a pound of steak had barely more effect than did the ingestion of a quart of milk. A pound of bananas or a quart of orange juice showed no effect on the acid-base equilibrium.

Morgan and her colleagues[20] studied the response of newly weaned puppies to the ingestion of diets of casein, agar, sucrose, suitable sources of vitamins, and various salt mixtures; the latter were acidic, neutral, and basic. Some animals received vitamins A and D in the form of cod liver oil, while others received only their vitamin A as butterfat. The significance of all the findings is not apparent, but they tend to show that cod liver oil is least necessary when the ash of the diet approaches neutrality and is most needed and most effective with an acid ash diet. The serum chemistry reflected in its changes the nature of the salt mixture employed, but the changes were of minor degree. Low calcium diets led to bone lesions which were more marked than were observed under any other regimen.

Sherman[1] and Harris[2] both state that the clinical significance of shortage of vitamin B in the ordinary diet is much less important than that of vitamin G. Harris emphasizes the frequency of vitamin D shortage in England; Sherman feels that the overexploitation of that vitamin in this country has been unfortunate, leading to an exaggerated sense of its importance in nutrition. Equal emphasis should be placed on the adequacy of intake of calcium and of phosphorus.

Hess[21] studied the incidence of night blindness as observed by ophthalmologists, and from the low incidence reported he concluded that deficiency of vitamin A is not particularly common. Jeans and Zentmire[22] studied the degree of dark adaptability in a large series of apparently healthy children and found a high percentage of subclinical night blindness, which was corrected through the administration of vitamin A. From their study they are led to believe that there is a widespread deficiency of vitamin A in the diets of children. The significance of vitamin A in relation to infection received the attention of many investigators. Hess[21] states that respiratory infections of infants are not due to deficiency of vitamin A and usually their incidence cannot be lessened by the use of a diet rich in that factor. His subjects, however, were not observed under conditions of low vitamin A intake. Clausen[23] and Robertson[24] have reviewed recently the relationship of nutrition to infection, and their conclusions are similar. Clausen states that susceptibility to infection is not as a rule affected by diet, while resistance to infection may be greatly reduced by deficient diet. The effects of deficiency of vitamins A and C are noteworthy in this regard, and under certain conditions inadequacy of vitamin B may exert a similar effect. According to him, a similar relationship for vitamin D has not been established. Robertson correlates the clinically observed value of vitamins in the prophylaxis against infections with possible suboptimal amounts of these in the diet. Although susceptibility does not seem to be altered thereby, the subsequent course of the infection seems to be modified. If the storage and ingestion level of vitamins already is at an optimum level, little may be expected from further additions; the difficulty lies in the fact that optimum levels for the various vitamins remain to be determined. An experimental study by Greene[25] shows that some alterations in serologic characteristics can be obtained through variation in the level of vitamin A available. Rabbits depleted of vitamin A were found less able to produce immune bodies to erythrocytes of sheep or oxen than were well-fed controls or those depleted of vitamin D. A smaller and possibly insignificant difference was noted in the ability to produce agglutinins for injected *B. typhosus* organisms.

Studying a group of over 200 women and children who were living under decidedly unfavorable dietary conditions, Brown, Campbell, Stoner, and Macy observed the effect of adding to the diet 3 gm. of non-fermenting yeast daily. They report that beneficial results were obtained as seen in gain in weight and lessening of anorexia and of constipation. No undesirable effects were noted.[26] The foods employed by these subjects were deficient in many of the essentials for normal nutrition, including vitamin B. Whether similar results might be expected through supplementing less limited diets with yeast remains open for question.

With subclinical degrees of vitamin C deficiency in mind, Dalldorf[27] studied the ease of production of petechial hemorrhages through the application of reduced atmospheric pressure, employing the technic described by Hecht. The apparatus used consists of a glass cup with an inner diameter of 1 cm., and with a flange of 8 mm. width, connected with a device for producing negative pressure and with a manometer. The pressure at which petechiae appear is noted; the standard for each individual must be known, since wide variations in capillary resistance seem to characterize different persons. For this reason, isolated readings offer little or no significance. The values observed in 251 children ranged from 10 to 50 mg. mercury, with an average value of 30 to 40 mg. Among a group of fifty-four children living under adverse economic conditions, the average pressure at which petechiae first were observed was 25.4 mg. of mercury, although over 9 per cent had values of over 50 mg. Successive measurements were made in fifty-two children, before and in the course of improved diet. Their initial average values were 22 mg.; after several months of hospitalization, the averages were up to the level observed in the other children in the hospital. Two children observed daily showed rapid increase in capillary resistance. A rapid improvement might be expected when vitamin C deficiency is corrected, as a corollary of histologic studies of animals studied similarly. The author states that apparently healthy guinea pigs frequently show evidences of scurvy at their costochondral junctions and that twice as much vitamin C is needed to prevent lesions in the incisor teeth of guinea pigs as is necessary for avoidance of frank scurvy. Fragility of capillaries appears in these animals within forty-eight hours after inauguration of low vitamin C diet. Presnell[28] found that the blood of scorbutic guinea pigs has a prolonged clotting time, fewer platelets and red corpuscles, and less hemoglobin than their normal controls. These findings antedate any other manifestation of scurvy in these animals but offer no data for humans. The rabbit does not show similar changes after twice the period needed for their production in the guinea pig. Greene[29] employed the negative pressure test on children's skin, as described above, studying well-nourished preschool children as subjects. He considered the test positive in 22 per cent of the group. The test was also positive in 9 per cent of a well-nourished group of older children, as compared with a positive incidence of only 8 per cent of a group of malnourished children receiving only a small amount of vitamin C. He emphasizes that a positive capillary test cannot be considered pathognomonic of vitamin C deficiency. The identification of vitamin C as ascorbic acid and its availability in concentrated form in various foodstuffs have led to the appearance of ascorbic acid on the market in pure form, suitable for administration either by mouth or parenterally. In

health no such measures need be employed, however, since adequate intake can be offered in the form of naturally occurring foods.[30]

Much confusion still exists regarding the relative value of various sources of vitamin D, and at the present it is not possible to draw clear-cut conclusions on the subject. The issue is made more acute through the appearance on the market of numerous foods enriched with "the sunshine vitamin." Sherman's remarks concerning the overexploitation of vitamin D are pertinent in this connection.[1] It is easy to focus attention on this one food essential to the exclusion of others equally worthy of consideration. In general, it probably is very desirable to supplement the intake of vitamin A in a degree parallel to that of vitamin D since often their potential deficiencies run parallel and evidence is accumulating to point to the advantage inherent in the use of vitamin A in amounts greater than those needed to prevent obvious disease.

Various authorities have offered estimates as to the quantitative dietary requirements of mankind. Many of these consider only the adult and will not be discussed in this review. British dietary authorities[16] asked to state as nearly as possible what a safe standard dietary would offer, stated that a desirable daily caloric intake should range from 900 to 1,100 calories during the first two years of life, 1,400 to 1,700 during the third to sixth year, with progressive increase up to 3,000 to 4,000 calories for the adolescent boy, or 2,800 to 3,000 for the adolescent girl. The need for protein consumption in greater amounts by the growing child than the adult is emphasized, also that much of this should be supplied as "first-class" protein, or that which approximates the composition of the body tissues most closely. The value of milk in this connection is stressed. McKay and Evans[31] observed the intake of children of preschool age and determined that their daily protein intake was equal to about 2.7 gm. per kilogram body weight or to 1.1 gm. per inch of height. Half of this was supplied by milk, 19 per cent by cereals, 19 per cent by meat and eggs, and 9 per cent by fruits and vegetables. About 13 per cent of the calories were supplied as protein. They remark that this intake seems consistent with the maintenance of health and good physical development. Sherman[10] emphasizes that animal or human organisms may grow to maturity with bodies poor in their content of calcium or of iron if the content of these minerals in the diet is suboptimum; yet such individuals may appear well nourished. Balance studies show that the amount ingested may exceed excretion in the child receiving as little as 0.4 to 0.46 gm. of calcium a day, but twice this intake is necessary if optimal retentions are to be observed. Such values are most readily attainable through the daily ingestion of a quart of milk. The desired ratios of calcium to phosphorus in the diet may show wide variation, because of the relative rate of growth of bone and muscle, each of which requires phosphorus for its composition; however, if the dietary intake of calcium and of phosphorus is liberal, no further attention need be paid to the ratio of one to the other in the diet. Sherman also notes that a liberal intake of calcium seems to aid in the conservation of iron, a mineral the metabolism of which usually is considered as wholly distinct from that of the former. He implies that as knowledge is gained, further interplay of function will be detected between various dietary components.

Wait and Roberts[32] observed the food intake of a group of well-nourished girls aged ten to sixteen years and computed the amounts of

various dietary factors ingested. Total calories varied from 1,650 to 2,925 per day. Considerable variability in the energy intake of the individual was noted with free-choice diets, ranging from 10 per cent to 181 per cent, averaging 49 per cent. They emphasize that because of this fact, more than four days' observation must be included in evaluating the intake of a child. The average daily caloric intake per day was about 66 per kilogram of body weight for the prepuberal age, lessening progressively through the period of declining growth to a level of 38 calories per kilogram per day at the completion of adolescence. The protein intake paralleled this in large measure, from the level of 2 gm. per kilogram at eight to ten years to 1.2 gm. per kilogram at sixteen to eighteen years. Koehne,[33] in a similar study of girls from six to thirteen years of age, offered a standard dietary but allowed considerable choice as to size and number of servings and in some measure as to the dietary constituents. The diet eaten had an average caloric distribution of 14.3 per cent from protein, 43.2 per cent from fat, and 42.6 per cent from carbohydrate. Each child was given about a quart of milk daily and as much butter as was desired. The calories per kilogram body weight per day ranged from 75 to 80 for the younger girls to 55 to 60 for the older ones; the corresponding protein intakes were 2½ to 3 gm. for the younger girls and 2 gm. for the oldest. The diets were basic; the average total daily intakes of calcium, phosphorus and iron for nine of the girls were 44 mg., 49 mg., and 0.44 mg., respectively. The author concluded on the basis of these observations that under suitable circumstances the child's appetite is an adequate guide for its food needs. Suitable circumstances in this study included the presentation of foods of high biologic value and surroundings conducive to their ingestion. Hubbell and Koehne[34] studied the retentions of calcium, phosphorus, and nitrogen by these same girls, under diets of the type described. These consisted of cereals equivalent to 15.8 per cent of the total calories; milk, 31.8 per cent; vegetables and fruit, 17.8 per cent; fats, 18.1 per cent; meat, eggs, cheese, etc., 11.4 per cent; sugars and sweets, 5.6 per cent; all expressed in the proportion of the total daily calories each item supplied. The average intake of calcium and of phosphorus was 1.4 and 1.5 gm., respectively. A second and third diet differed from this one in that sugar was added in amounts sufficient to increase the total calories by 6 per cent and sixteen to eighteen per cent, respectively. On the low sugar diet the average retentions of nitrogen, calcium, and phosphorus were 26, 5, and 7 mg. per kilogram of body weight per day. The second diet gave retentions practically the same as these, while with the high sugar intake there was reduction in the retention of calcium in five out of seven girls studied and a tendency to increased retention of nitrogen and of phosphorus. The retention levels observed in this study are lower than those considered desirable by some students of mineral metabolism.

Stearns[35] reported in abstract the summary of retentions of calcium by infants and children receiving various amounts of milk, with diets which otherwise were quite comparable. The infants and young children were given additional vitamin D. The age range included children from six weeks to twelve years. The infants retained as much or more total calcium than the older children for any given amount ingested. The lowest level of retention was in the group aged three to five years. The retention per unit of body weight was highest in early infancy, declining during infancy and early childhood. In all cases, higher retentions were

obtained when the intake was increased. The curves of daily retention levels per unit of weight plotted against the age of the subject paralleled closely the predicted curve of yearly increment in height.

In a study of the relative value of a pint as compared with a quart of milk a day in the child's diet, Daniels and her coworkers[36] determined the retentions of calcium, phosphorus, and nitrogen in children of preschool age on the two levels of calcium intake as supplied by those amounts of milk. They noted a wide variation in the amounts retained by children of the same age, and by the same child, when the two intakes were employed. Those children previously well fed retained less than those who initially had lower reserves of nutrition. They suggest that the physiologic condition of the children at the time of the test and their individual potentialities for growth apparently condition the wide variations noted in the retentions. However, they conclude that when the diet supplies sufficient protein, phosphorus, and vitamins from other sources, a child between the ages of three and five years can obtain sufficient calcium for its needs from a pint of milk daily. The retentions noted were 3 to 10 mg. of calcium, 6 to 8 mg. phosphorus, and 34 to 90 mg. nitrogen per kilogram per day.

Porter-Levin[37] observed retentions varying from 8 to 17 mg. calcium and 5 to 8 mg. phosphorus per kilogram body weight per day in children of similar age.

Boyd, Drain, and Stearns[38] correlated the retentions of children who had dental examinations made simultaneously, many children being reexamined on several subsequent occasions. All received diets high in the various protective factors. Correlations showed that highest retentions of calcium and of phosphorus were noted among the children whose teeth were free from decay, intermediate retentions in those whose teeth showed inactive decay, and least in those with active decay. The latter values, however, were as high as or higher than those usually accepted as normal, while those of the children with no caries had retentions averaging approximately 50 per cent higher than the group with active caries. The investigators question whether the usually accepted retention values may not be considerably less than the optimum.

The gap between familiarity with the nutritional needs of the body and the application of this knowledge to the practical feeding of children is not a great one. The factors involved include the availability of the various essentials in common and readily obtainable foods and the ability of parents to supply them and to administer them to the children in a suitable manner.

If attention is paid to the use of foods high in their content of protective factors, such as qualitatively valuable protein, calcium, and the various vitamins, the energy relationships usually need little consideration. Foods of the type mentioned include milk and its products, eggs, fruits and vegetables in variety and in liberality, and cod liver oil. While the latter may be omitted with safety when the diet otherwise is liberal, it enhances the value of a good diet and lessens the dangers of the limited diet. Morse[39] has recently reviewed the necessary requirements in a minimum diet for infants and children. While such limitations may be economically necessary, outstanding advantages are offered by the diet which is high in the various essentials for nutrition. While meats are desirable and advantageous in the child's diet, they should not be used to replace milk or other foods. Sherman[1] emphasizes that

grains are still the staff of life, and that if only a very moderate proportion of these is consumed as "whole," or slightly milled, the intakes of phosphorus, iron, copper, manganese, and vitamins B and E will usually be ample. Milk, fruit, vegetables, and eggs will meet the needs for calcium, phosphorus, and for vitamins A, C, and G easily, agreeably, and economically if eaten in moderately high percentage in the diet.

The economic aspects of adequate nutrition are of great importance at this time. An English authority[2] estimates that in England at present prices the minimal safe diet for an adult will cost $1.25 per week for raw food, and that for a young child the cost will be 75 cents. Desirable diets will cost correspondingly more. Because of this, he states that in certain communities adequate diets cannot be obtained. Yet much of the difficulty lies in the manner in which the money for food is spent. Hawley,[40] in an attempt to compromise between the limitation of money for food and the needs of the body, has suggested the following as a safe diet, approaching a minimal cost for safety: milk—2 to 4 cups as such for each child daily, one cup for each adult, one milk dish daily for the entire family; cereal—daily for breakfast, and in some form again during the day; one of these should be as whole grain; fruit—three times weekly; dried prunes, peaches, or apricots once a week; potatoes—usually once a day, or oftener if desired; vegetables—two daily, as soup or as salad; tomato—daily for children, three times a week for adults; eggs—two or three a week for very small children, daily for those over two years if possible; legumes—once a week; cheese, fish—once a week; butter—once daily, the remainder of table fat may be served as oleomargarine; meats—two to three times a week, daily if desired and if possible; liver, heart or kidney should be served once a week; cod liver oil—daily for all preschool children, for all who are underweight, for those on special diets, and when prescribed by the physician. Through aid in food budgeting and through the aid given by relief agencies, the health and nutrition of those children so supervised have been reported to be at higher levels than heretofore.

Among the more favored economic groups, the problem of wisdom in choice of food frequently is as assertive as among the poorer classes. In addition, the psychologic aspects of child feeding are decidedly more in evidence in the former than in the latter group. Hunger strikes, poor appetite or anorexia, and similar difficulties often outweigh all other phases of the practice of nutrition with these children. No agreement exists as to the best measure for correcting these psychologic barriers to good nutrition. Such attitudes may be credited to the attitudes of the other members of the household, and if this and other aspects of the environment could be made ideal, much of the difficulty would be prevented. Contributing factors in the mental set of the child toward his food include the example as to eating offered by the other members of the household; differences of opinion concerning food needs; outstanding and loudly expressed dislikes for certain foods; the desire of the child to assert himself through his food habits or to gain his share of attention in the table conversation; the overzealous and often misguided efforts of the mother to make the child eat. Certainly it is most essential that the eating of suitable food be made a matter of course, and one devoid of emotion or display of force. The manner of attack is the question to be answered. Many proponents urge that the diet of the child be left to his free choice, and data have been presented in the foregoing

to show that such a regimen may be nutritionally satisfactory. Various studies of the quality and quantity of food ingested under free choice have been published, with more or less critical attitude on the parts of their authors as to the adequacy of the diets chosen. Aldrich[13] states that the normal child will eat enough food for adequate nutrition if it is offered to him in an intelligent manner, in an attractive form, and without undue urging and that the properly handled average child of twelve to eighteen months should be able to feed himself all important foods. Once this is accomplished, the child should be left to his own responsibility regarding his feeding, without suggestions as to the type or amount of food, or the speed of eating. Solicitude may lead to anorexia with negativism to the intake of the foods most urged, which usually will be those considered the most important. However, the crux of the whole system is the offering of only those foods which are qualitatively adequate. In other words, for such a regimen to succeed, the parents must have greater insight than usually is displayed concerning the types of foods of value in nutrition; the child should eat under conditions free from distractions, in a pleasant environment. The child must not be credited with any uncanny ability to sense his nutritional requirements. Harris[9] reminds us that the baby with rickets has no instinctive craving for cod liver oil; the high incidence of evidence of rickets throughout most of the northern climates speaks against the safety of a self-choice regimen. The same investigator has studied the instinctive ability of animals to choose their own diets wisely and has found that only when a change in diet is immediately beneficial will a rat adopt a desirable change. He states that correct nutrition cannot safely be left to instinct, or to the use of "natural unspoiled foods," or to a varied diet, or to a process of free selection. Some form of desirable motivation is necessary to direct the child into suitable habits of diet. Hamill[14] expresses his opinion that the nature of a self-selected diet will be dictated by the appetite rather than by the immediate physiologic needs. While life undoubtedly would continue on a self-choice type of dietary, as it has done for countless generations, the safety of such a regimen will be in relation to the intellectual and economic adequacy of those administering it; moreover, the conscious improvement of the level of health which designed nutrition permits will not be achieved readily, if at all, under such conditions.

The answer seems rather to lie in the dissemination of ideas concerning the interdependence of radiant health and the nature of the food intake, and the relative values of various foods. Then, if the whole household will consider food as a physiologic necessity rather than merely a means for pleasing the appetite, a compromise may be effected between the free choice of a diet from the substances wisely offered and the wise supervision of the whole dietary. The success of such a regimen is exemplified in those children who because of diabetes mellitus are placed on a rigid form of diet, complete in all regards; and who, having adjusted themselves mentally to such discipline, enjoy the regimen and exhibit a nutritional state which is superior to that of their brothers and sisters whose nutrition is left to their own direction.

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American Academy of Pediatrics

Proceedings

FOURTH ANNUAL MEETING OF THE AMERICAN ACADEMY OF PEDIATRICS

JUNE 11, 12, 1934

Round Table Conference on Syphilis

Leader: Dr. Joseph Yampolsky, Atlanta, Ga. Assistants: Dr. M. Hines Roberts, Atlanta, Ga., and Dr. Lemuel R. Brigman, Cleveland, Ohio.

The Round Table Conference on Syphilis held at the Wade Park Manor Hotel, Cleveland, was called to order by Dr. Joseph Yampolsky, chairman.

CHAIRMAN YAMPOLSKY.—This discussion will take up the treatment of syphilis in children. Dr. Roberts will speak on "The Transmission, Occurrence, and Behavior of Congenital Syphilis," with emphasis on the treatment. Dr. Brigman will discuss "The Untoward Effects of the Use of Arsenicals in Children," and I will discuss the many and various preparations used in the treatment of this disease.

Treatment of Syphilis in Children With Special Emphasis on the Use of Stovarsol

Joseph Yampolsky, M.D.

Today syphilis in children is more easily recognizable; therefore, more cases are seen and are amenable to treatment. This is true especially in children born of known syphilitic mothers, without the children themselves manifesting symptoms of syphilis or in those whose diagnosis is assured only through a positive Wassermann reaction.

Starr[1] in his textbook, *Diseases of Children*, as early as 1894 stated that the treatment of hereditary syphilis must be conducted in accordance with those principles which govern the therapy of acquired syphilis in adults with such modifications as are demanded by the age of the patient. The treatment at that time consisted primarily of the use of mercury and iodides in one form or another. As late as 1924, Veeder[2] in Abt's *Pediatrics* stated that three drugs are in common use in the treatment of syphilis in children, viz., arsphenamine products, mercury or one of its salts, and potassium iodide. However, drugs are constantly added to our armamentarium in the treatment of this disease. At present besides those mentioned, two new drugs in the form of bismuth and stovarsol have been added and also the infrequent use of a combination of bismuth and arsenical preparations in the form of bismarsen.

In outlining the treatment of syphilis, we might consider Wegner's[3] general rule in application of medications used. The treatment depends on the following formula:

1. The variety of the clinical symptoms and their percentile distribution over various ages (infancy up to the age of one year, young children from 2 to 5 years; school age from 6 to 13 years; adults over 14 years of age).

2. The effect of the treatment in the various ages.

3. The results in the cases which became negative and in which the follow-up examination revealed negative clinical and serologic pictures.

4. The fate of the patients who did not become negative in spite of the "chronic," continuous treatment.

5. The duration of the treatment.

Arsenical Drugs

The most common arsenical drugs used are arsphenamine and neoarsphenamine. While the weight of evidence is in favor of arsphenamine, neoarsphenamine is more useful in children because of the ease of administration.

Neoarsphenamine.—Neoarsphenamine does not have to be neutralized and may be given intramuscularly with safety; one-half dose can be given in each hip with little pain and little chance of abscess formation. It is given deeply but not under the aponeurosis. It is given in the upper part of the buttocks or external surface of the thigh. Two injections are made each week with a total of fifteen injections.

The following method[6] of treatment in a case of syphilis has been used at Emory University School of Medicine. A course of sixteen injections of neoarsphenamine alternating weekly with mercury salicylate or bismuth is given. The dosage is 0.02 gm. of neoarsphenamine dissolved in 0.4 c.c. (six minims) of freshly distilled sterilized water given either intravenously or intramuscularly for every 3 pounds of body weight. When the intramuscular injection is used, one-half of the dosage is given in each buttock and hot compresses are applied to the buttocks for one-half hour after the treatment. Mercury is given in the form of a suspension of mercury salicylate in olive oil or cold cream intramuscularly; and the dosage is 0.5 grain to 30 pounds of body weight. After the sixteen weeks of treatment, a thirty-day rest is given when the Wassermann test is made. If the Wassermann reaction is negative, the patient rests for sixty more days and then a complete course of treatment is given again. If the Wassermann reaction is positive, a complete course is begun immediately, but mercury is omitted completely and bismuth used instead. No more treatment is given during the first year of observation. After the second course an examination of the spinal fluid is made. Wassermann reactions become reversible when treatment is begun very early in infancy and especially in those who have positive serologic reactions only. Later in life it is difficult to reverse the Wassermann reaction.

Arsphenamine.—Arsphenamine should never be used intramuscularly. Silver arsphenamine has not been employed very much in the treatment of congenital syphilis, and even in adults it is used more often in neurosyphilis. Sulpharsphenamine may be used in children over five years of age because of the ease of administration and the absence of after-effects. In the cases in which treatment was instituted early, the greatest number of cures were obtained. Serologic reverses were obtained in practically all children under five years who stayed for at least one year's treatment. When treatment was inaugurated at a later age, the response became less satisfactory as the age of the patient advanced. In the older cases mercury and the arsenicals are needed over so much longer a period of time that one must consider the toxicity of the drugs as well as the disease itself. Slow arsenic and mercury poisoning must at least be kept in mind in cases in which treatment is necessary over a long period of time. When arsphenamine is used by the syringe method, it may be diluted in as little as 0.1 gm. in 4 c.c. of water. A safe dilution of the neoarsphenamines is about 0.1 gm. to 2 c.c. of cold, freshly distilled, sterilized water.

Intraperitoneal Method.—The use of neoarsphenamine intraperitoneally is worthy of trial if difficulty is found in injecting arsenicals intravenously and if syphilitic manifestations are so acute that a method must be found for the quick absorption. We[4] have reported a study of seventeen cases. Before starting treatment on the children, we injected several rabbits intraperitoneally, giving 0.02 gm. of neoarsphenamine for every 3 pounds of body weight diluted in 0.4 c.c. (6 minims) of freshly distilled, sterilized water for a full course of treatment. No bad results were encountered at any time. After many months an autopsy was performed, and there were no signs of adhesions or peritonitis. Some of these rabbits were submitted to autopsy shortly after the injection of the drug. The absorption was almost immediate, and the peritoneum was glistening and normal in every way. After a full course of treatment for the children a gastrointestinal x-ray examination was made on the first two patients. No ill effects were noticed along the whole intestinal tract, and no adhesions were present.

We present the following summary:

1. In seventeen cases of congenital syphilis covering a period of over four years, patients were given from sixteen to thirty-two intraperitoneal treatments, and in one case, eight. Only four of these patients present positive Wassermann reactions after treatment, but no patients present any signs of congenital syphilis.

2. Both neosalvarsan and mercurosal were given intraperitoneally; these caused no deaths, no peritonitis, or adhesions, as shown by experiments on rabbits. There was no bad effect on human beings as shown by x-ray and fluoroscopic examination.

3. Absorption is rapid from the peritoneal cavity, and if the injection is made with proper aseptic technic, it should be attended by no bad sequelae.

Mercury

Mercury is the oldest preparation used for the treatment of congenital syphilis. Mercury salicylate has been used extensively; 0.5 grain for every 30 pounds of body weight can be given intramuscularly. Another preparation, bichloride of mercury, can be given either by intramuscular injection, the dosage being 0.033 c.c. of a 1 per cent solution per kilogram of body weight or by mouth in the form of gray powder, the dosage being 0.2 grain twice daily to infants up to 2 grains three times daily in older children. The ease with which the veins may be sclerosed should keep us from resorting to the intravenous use of mercury. Mercury has been used by inunctions in very young infants. This is usually given in the form of mercurial ointment. The dose is from 15 grains up to 1 dram. The inunctions are given in different parts of the body to avoid irritation. Mercury may also be given to the lactating mother as a safe and accessory form of treatment. The use by inhalation of mercury is of no value.

Bismuth

Bismuth has been used with success in both acquired and congenital syphilis. The summary of Sutton[6] is most interesting. He said that bismuth seems especially useful for patients who become intolerant to arsenicals when one cannot resort to mercury. In old, treated syphilis the field of action of bismuth is applicable because of its breadth—because arsenic becomes devoid of action and is poorly tolerated as a result of a sensitization on the order of anaphylaxis which develops.

It is advisable to use bismuth intramuscularly and not intravenously. Oral and dental examinations should be made constantly during this course of treatment, and a urinary examination should be made for the presence of albumin.

Quiniodobismuth is one of the valuable compounds of bismuth. The others contain more bismuth, but the addition of quinine and iodide reinforces its action. The soluble salts, permit precise dosage, a greater absorption, and a regular action. Its efficiency is equivalent to that of the insoluble salts but necessitates a greater fre-

quency of injections because of the rapid elimination of bismuth. The most common salts used in this country are salicylate of bismuth, bismuth sodium tartrate, and quiniodobismuth.

The Council on Pharmacy has warned against the intravenous injection of bismuth salts, and it would seem that, when a preparation can be given into the muscles, its intravenous injection would expose the patient to needless risk. Nitritoid crises have been reported following the intravenous injection of soluble bismuth compounds, and cases of sudden death have occurred when an insoluble suspension was injected accidentally into the circulation.

Bismarsen

The most comprehensive study of the use of bismarsen in children has been reported by Chambers and Koetter.[7] These authors used bismarsen in 180 children and infants observed for periods varying from one to two and one-half years. A total of 6,349 injections have been given to date. The ages varied from birth to fourteen years of age, the majority being three years old.

A complete serologic reversal occurred in 51 per cent; in 41 per cent the reaction remained unchanged; 8 per cent showed ultimate reversal. The Wassermann reversal occurred by the tenth week in 4 per cent, by the twentieth week in 25 per cent and by the fortieth week in 41 per cent. No relapse occurred in any other clinical form except in interstitial keratitis.

Iodides

The iodides should be used only in cases of late hereditary syphilis since they have little effect upon the *Treponema pallidum* but may be useful in aiding the absorption of exudative gummatous processes. The drug is not well tolerated by nurslings and often causes a coryza which interferes with nursing. Potassium or sodium iodide is usually used, and the dosage from 0.2 to 0.05 gm.

Stovarsol

The experimental use of stovarsol in spirochetal and trypanosomic infections was first published by Fournier in 1921. This preparation is also known as "acetarsone" or "spirocid" by the Germans. Stovarsol contains from 27.1 to 27.4 per cent of arsenic and is chemically known as acetylaminohydroxyphenylarsonic acid. It is furnished in 0.1 gm. and 0.25 gm. tablets. A 0.25 gm. tablet contains approximately 0.0068 gm. of arsenic while an 0.1 gm. tablet contains approximately 0.0027 gm. of arsenic.

The medication may be administered as outlined in Table I.

TABLE I

PERIOD	DURATION OF PERIOD	DOSE OF STOVARSOL DAILY PER KG.
First	7 days	0.005 gm. 1/13 grain
Second	7 days	0.010 gm. 1/7 grain
Third	7 days	0.015 gm. 1/4 grain
Fourth	7 days	0.02 gm. 1/3 grain
Fifth	5 weeks (5th, 6th, 7th, 8th, 9th weeks)	0.02 gm. 1/3 grain
Sixth	6 weeks	none (rest for 6 weeks)
	Duration of entire active course	9 weeks
	Duration of rest period	6 weeks

If the Wassermann reaction is positive, no rest period is given; treatment is begun with usual dosages during the first week, to be continued for nine weeks as shown in Table I.

Some authors claim that it is best to administer one dose daily. We have used the daily dose divided into three equal parts given in milk or water one-half hour before meals. Since stovarsol is rapidly decomposed in an acid medium, free arsenic is liberated to be rapidly absorbed in the body.

The reactions to the use of stovarsol may be summarized as follows:

1. Eruption of a scaly nature over the body
2. Diarrhea
3. Hyperpyrexia
4. Pyuria
5. Nephritis
6. Death

Other authors report Herxheimer's reaction and albuminuria. The medication should be discontinued at the first signs of sensitivity to the drug, though in a short while treatment may be resumed.

Our routine treatment is as follows:

1. Wassermann reaction is taken before and after treatment.

2. Complete blood examination is made when possible before and after treatment.

3. X-ray examination is made of all long bones and of fingers and toes before and after treatment.

4. Urine specimen at least twice during treatment is collected and examined macroscopically and microscopically.

5. Temperatures are taken only if there is some suspicion of fever.

6. Weight is recorded on every visit to the clinic.

7. Spinal puncture is performed, and Wassermann test and globulin and cell count are made on spinal fluid in every case at the end of the treatment.

The results of the Wassermann tests are reported in Table II; urine examinations

TABLE II

NO.	BEFORE TREATMENT		MOTHER'S WASS.	AFTER TREATMENT	
	AGE	BLOOD WASS.		BLOOD WASS.	SP. FLUID WASS.
153746	7 wk.	++++	neg.		
155678	8 wk.	++++	neg.	++	neg.
1__020	8 wk.	++++		neg.	neg.
151187	11 mo.	++++	++++	++++	neg.
153011	18 mo.	+++		neg.	neg.
146806	19 mo.	6/15/32 neg.		++++	neg.
		10/ 7/32 ++++			
153036	3 yr.	Wass. fast ++++		neg.	
152607	3 yr.	++++		neg.	neg.
119145	5 yr.	++++		++++	neg.
151159	7 yr.	8/ 9/32 neg.			
		8/22/32 ++++			
150645	8 yr.	1925—++++			
		1933—++++		neg.	neg.
135845	9 yr.	++++			
119136	10 yr.	Wass. fast		++++	neg.
148421	10 yr.	++++		++++	
153087	11 yr.	++++		++++	neg.
154114	11 yr.	++++		++++	neg.

were negative in all cases except one in which there was transitional pyuria; blood counts are reported in Table III; clinical findings, in Table IV; x-ray findings, in Table V.

TABLE III

	BEFORE TREATMENT			AFTER TREATMENT		
AGE	HG. %	R.B.C.	EOS. %	HG. %	R.B.C.	EOS. %
7 wk.	50	2 plus	5	60	3 plus	3
8 wk.	66	3 plus	2	65	3 plus	5
8 wk.	66	3 plus		75	3 plus	3
11 mo.	55	3 plus		55	2 plus	
18 mo.	55	4 plus	1	65	3 plus	
19 mo.	60	3 plus		60	3 plus	
3 yr.	65	3 plus	2			
3 yr.	80	4 plus	5			
5 yr.	80	4 plus	4	70	3 plus	
7 yr.	60	4 plus	4			
8 yr.				75	4 plus	
10 yr.	75	4 plus	6			
10 yr.	80	4 plus		85	5 plus	2
10 yr.	90	5 plus	3			
11 yr.	80	5 plus		85	3 plus	
11 yr.	80	4 plus	2	85	4 plus	

TABLE IV

CLINICAL FINDINGS

AGE	BEFORE TREATMENT	AFTER TREATMENT
7 wk.	Painful swelling of thighs and knees	Improvement in ability to use legs
8 wk.	Peeling of palms and soles and inability to use limbs	Able to use arms and legs; skin lesions improved
8 wk.	Swelling and tenderness right elbow	Improved
11 mo.	Snuffles, malnutrition	Improved
18 mo.	Anal condyloma	Improved
19 mo.	Palpable cervical lymph nodes, malnutrition	Improved
3 yr.	Maculopapular rash on trunk and extremities	Improved
3 yr.	Vulval condyloma, palpable cervical glands	Glands improved; condyloma improved
5 yr.	Snuffles with nasal swelling	Slightly improved
7 yr.	Interstitial keratitis; bursitis, both knees	Improved
8 yr.	In 1925 epiphysitis right femur, no treatment; in 1933 swelling and pain in both knees	No improvement until after 7 wk. of treatment
9 yr.	Cervical adenitis	Marked improvement
10 yr.	Generalized adenopathy 1929 Wass. fast 1933	No improvement
10 yr.	Swelling left knee, no pain	Improved
11 yr.	Keratitis perforation in roof of mouth, snuffles	Keratitis improved greatly; snuffles disappeared
11 yr.	Keratitis	After 2 courses of treatment, very little improvement

Our conclusions are as follows: Oral treatment of syphilitic children is coming back into use because of the advantage of such medication. Although negro children show very little toxicity to this drug, it is important not to use the medication indiscriminately. The disappearance of skin lesions and the general improvement of the patients make us feel favorably disposed to the use of stovarsol.

TABLE V

X-RAY FINDINGS*

AGE	BEFORE TREATMENT	AFTER TREATMENT
7 wk.	Periosteal thickening of long bones; increased density of epiphyses	
8 wk.	Slight destruction upper ends of both ulnas, lower end right radius	Definite periostitis in bones of lower extremities; improved left elbow
8 wk.	Periosteal thickening upper end of right ulna	Improvement in long bone lesions
11 mo.	Periosteal thickening of long bones; increased density at diaphyses	No material changes observed
18 mo.	Diaphyseal erosion; cross-sections of increased density in femurs	Nearer normal density; slight erosion at lower ends of both tibia
19 mo.	Bone destruction both ends of bones of forearms; syphilitic osteomyelitis	Not obtained
3 yr.	Erosion of lower epiphyses of femurs; periosteal thickening of radii	Not reported
3 yr.	Expansion of diaphyses of long bones	No change in bone lesions
5 yr.	Periosteal thickening of margins of long bones	No definite changes
8 yr.	Epiphyseal separation of lower end of right femur	No definite evidence of syphilitic involvement
9 yr.	Slight periostitis along shaft of left radius at wrist	Not reported
10 yr.	Marked periostitis of both tibia and fibula	Tibias slightly sabered. Periosteal reaction anterior border of left ulna
11 yr.	Periosteal thickening at lower end of femurs	Periostitis lower end of diaphyses both femurs; progressive syphilis

*Three cases were negative before and after treatment.

This is also true in the serologic reactions, and especially in our cases of the reversal of the Wassermann reactions in the Wassermann-fast cases. The roentgenologic results have not been gratifying. The status of stovarsol is still not definitely known. We do not believe that this drug per se without the use of other medications can cure syphilitic lesions of bones and many other late lesions of congenital syphilis, but we certainly agree with other writers that stovarsol has a definite place in the treatment of this disease.

Treatment of Neurosyphilis

If after a year's duration of the ordinary antisyphilitic treatment the patient still has signs of neurosyphilis, it is advisable to use intraspinal treatment, though in our experience treatment has not been successful. We wish to describe the injection of arsphenaminized serum in neurosyphilis. One-half hour after the intravenous injection of the arsphenamine, serum is obtained from the blood and from 10 to 25 c.c. (according to the size of the child) is given intraspinously. This serum may be inactivated at 56° C. for one-half hour in order to increase the efficacy of the drug. The same amount of spinal fluid is then withdrawn and the serum injected into the spinal canal. Occasionally the arsphenaminized serum may be further fortified by the addition of arsphenamine before injecting it into the spinal canal. Veeder[2] occasionally adds 1 or 2 mg. of mercurochloride before inactivation.

Solomon and Epstein[9] inject hypertonic solutions of saline intravenously six hours before the injection of the arsenical preparations through the same route. A spinal fluid examination reveals that the arsenical content is much increased in these cases.

Malarial Treatment

The use of this treatment for interstitial keratitis may also be used in neurosyphilis in children, occasionally with some remission of symptoms.

Use of Tryparsamide in Treatment of Neurosyphilis

Let us report briefly an opinion of Reese[10]: "The disappointing response to Ehrlich's compounds, arsphenamine and neoarsphenamine, in neurosyphilis has caused clinicians to take a pessimistic view. Arsphenamine changes the biology of the spirochete, consequently modifies the histopathologic effects of the virus, and produces a clinical entity meager in symptoms. Without arsenical therapy a large number of the metasyphilis of today would be the tertiary syphilis of the past. We do not agree with statements in the literature that arsenical therapy alone is responsible for the increase of general paralysis and tabes dorsalis. The steadily increasing curve of general paralysis for both sexes is not the result of insufficient antisyphilitic therapy but is due solely to the increase of recognized syphilis."

Tryparsamide is the sodium salt of the amide of the phenylglycine-p-arsonic acid, obtained by replacing the hydroxyl group of the carboxyl with the amide group. Tryparsamide has a very feeble spirocheticidal activity. It is inert in the first and second stages of syphilis, in syphilitic aortitis, in tabetic arthropathies, and in tertiary manifestations in general, which fact precludes its therapeutical use in these types, but it gives best results in the meningovascular type of neurosyphilis.

The dose of tryparsamide is 0.04 gm. per kilogram of body weight, that is, an average of 3.0 gm. in adults or 2.0 gm. in small children. Tryparsamide must be used over a period of months and years and cannot be judged by the effect of one, two, or three courses. The addition of mercury results in more permanent improvement of the serologic findings, as well as a more rapid and prolonged clinical benefit. As a practical routine, we recommend from eight to sixteen injections to be given at weekly intervals, combined with mercury or bismuth preparations. Tryparsamide medication is followed by a decided gain in weight and by improvement in the physical condition, indicating a great stimulative effect upon the general metabolism. If a patient under tryparsamide treatment does not gain in weight, the prognostic outlook is doubtful, if not poor.

There is general agreement that the effect on the pleocytosis is prompt.

A summary of our serologic results reveals:

Blood Wassermann:	40.2%	negative
	35.5%	reduced
	16.2%	unchanged positive
Spinal fluid Wassermann:	25.7%	negative
	47.0%	reduced
	27.3%	unchanged positive

The statement referred to in all reports that tryparsamide is a menace to the optic nerve, causing toxic amblyopia, necessitates comment. If careful examinations of the eyes are made before and during treatment, most of the ill effects can be avoided.

CONCLUSIONS

Apparently many drugs are used in the treatment of syphilis in children. Many methods have been described for consideration.

The problems for discussion should be as follows:

1. What drugs are most effective in the use of the different stages of congenital syphilis?

2. What method of procedure is to be employed in deciding the length of treatment?

3. Should arsenicals be used without the aid of metallic salts? This is of especial importance in the use of stovarsol.

4. How long should one wait before treatment is given to a child born of a syphilitic mother although the child is clinically and serologically negative at birth?

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DISCUSSION

DR. BRIGMAN.—Can you reverse the Wassermann reaction when it remains positive under stovarsol by using salvarsan with mercury or salvarsan with bismuth? I have given stovarsol in old treated cases rather than in the untreated cases. I have found a number of Wassermann-fast cases which after one or two courses of stovarsol showed a reversed Wassermann reaction. I have had no ill effects from stovarsol except mild diarrhea, which disappeared on stopping the drug, and one or two cases of mild pruritus.

Skin lesions disappear after stovarsol almost the same as after salvarsan, arsenic, and bismuth, but the bone changes do not disappear as rapidly. This suggests that stovarsol has a greater effect on skin syphilis than on bone syphilis.

I have just started a new plan. In other words, what I tried to do, instead of giving the rest period according to the Bratusch-Marrain outline and then another course, I follow the two courses concurrently and have doubled the time, which gives a longer treatment without ill effects from the drug. Whether the Wassermann reaction becomes negative sooner, I do not know.

CHAIRMAN YAMPOLSKY.—Do any of you give arsenical drugs gradually in syphilis in children?

DR. E. G. PADFIELD (SALINA, KAN.).—I have seen cases of keratitis treated by combined therapy with fairly satisfactory results; a few were not so good, but they were apparently better than were reported from stovarsol. I have been wondering if we are coming back to our old treatment of keratitis, considering the results which are obtained from stovarsol.

CHAIRMAN YAMPOLSKY.—The question of rest is important. Some authors agree we should have a rest period, and others think a rest period is not wise. In an older person we usually give iodides, but they are of no benefit in young children, especially in sucklings.

DR. BRIGMAN.—I alternate the treatment of my cases, one gets bismuth and the next salvarsan, neosalvarsan, or sulpharsphenamine. The next patient will get

bismuth and salvarsan, and the next one, stovarsol so that we have at the same time a group of patients who will show about the same results. We will learn more from our results than from mapping out an objective and then trying to reach it by some particular form of treatment.

We had an opportunity to study congenital syphilis in a very large number of patients, and have become interested in the transmission of the disease and its development. It has so many peculiar phases and apparently many controversial methods of behavior. The very name of the disease (whether it is hereditary or congenital) has been in controversy for many years. At the old Babies' Hospital we made a careful examination of the patients whose history suggested syphilis, and we found 3 per cent with a positive Wassermann reaction. This group was made up mostly of colored infants and a few of foreign parentage. However, when we took a Wassermann reaction of every patient regardless of what or who he was, our percentage increased about 1 to 1.5 per cent, so that 3 per cent was a general average.

DR. ROBERTS.—In our present studies the incidence of positive reactions is going to be somewhere around 5 per cent.

DR. W. P. McDOWELL (NORFOLK, VA.).—Ours is 7.5 per cent in an unselected group of patients, 65 per cent of whom are negroes.

DR. ROBERTS.—I should think the incidence among the negroes, exclusively, would be around 7 per cent. Would you expect it to be higher in infants than in older children?

DR. McDOWELL.—Our figures are rather high compared with the figures that have been given.

DR. ROBERTS.—We have observed twenty-eight babies who never showed syphilitic disease and who had positive blood tests which within three or four years became negative. Such a positive Wassermann reaction is probably due to the fact that the reacting substance in the mother's blood is transferred to the baby's blood for a short time and then disappears.

The Transmission Occurrence and Behavior of Congenital Syphilis

M. Hines Roberts, M.D.

The capricious behavior of the syphilitic infection in man, with its many apparently contradictory phases, stands as a constant challenge to the investigative mind. In no phase of the infection is this so strikingly evident as in so-called congenital syphilis. Even the name of this phase has been the center of controversy, for the implications of hereditary as opposed to congenital syphilis are of such importance as to influence our entire concept of the infection.

Two schools of thought have arisen as to the mode of infection, namely, transmission through germ cell—hereditary syphilis—and transmission by way of the placenta or birth canal—congenital syphilis. The obscure behavior of the infection accounts for this controversy. The appearance of syphilis in the offspring of a woman apparently free of the infection from the standpoint of history and physical or serologic evidence has made the diagnosis of congenital syphilis difficult of explanation. The fact that the spirochete is many times larger than the spermatozoon seems to make the theory of germ cell transmission physically impossible. These and other apparently contradictory phenomena have accentuated the argument.

Advocates of germ cell transmission hold that the spirochete is pleomorphic, that during certain stages of its life cycle it may exist as an ultramicroscopic granular body easily harbored by the spermatozoon. Certain work advanced by Burget and others seems to confirm this theory. Hochsinger claims undoubted paternal transmission in several cases followed in private practice for many years.

The apparent inconsistency of the normal healthy mother bearing a syphilitic child is explained by the group upholding placental transmission by the fact that syphilis may frequently pass through a latent or occult phase, during which the infection cannot be proved. This is especially true during pregnancy. It is fairly common observation that pregnancy appears to confer a certain immunity to the ravages of the spirochete. This may be seen not only in the recession of physical findings, but also in the reversal of the Wassermann reaction. It is believed, however, that these patients, if watched carefully over a sufficient period of time will invariably present clinical or serologic evidence of the disease.

As more data have been submitted, investigators in this field lean more and more to the theory of placental transmission of the disease. In his *Modern Clinical Syphilology* Stokes summarized as follows: "Most observers accent the maternal transmission of syphilis as the usual, if not the invariable, mechanism. They remain, however, open-minded to the possibility of a rest form of spirochete discovery of which may ultimately establish the possibility of paternal transmission. There can be no doubt that one meets from time to time clinical cases in which maternal transmission is, to say the least, obscure."

Moore, in his recent work on syphilitic therapy, reached a similar conclusion.

The incidence of syphilis in children is most difficult to determine accurately. Statistics vary widely, depending on the source of the material—whether hospital, out-patient, or private practice—whether cases have been studied intensively for this disease—whether the statistics are taken from a large unselected group.

Jeans and Cooke, in their excellent monograph, stated that hospital clientele of this country shows a syphilitic incidence among children varying from 2 to 3.5 per cent. If the age of patient is considered, it is found that the older the child the lower the syphilitic incidence, a fact probably accounted for by the higher mortality rates in the syphilitic group.

These authors report their findings in 62,815 children admitted to their out-patient service in St. Louis, over a period of thirteen years. Of this group of children, 1,202 were recognized as syphilitic, 1.9 per cent.

Since the incidence of syphilis in childhood is highest in infancy, Jeans and Cooke attempted a study of the infant population of St. Louis. They found that 15 per cent of negro infants were syphilitic at the time of birth, while 1.8 per cent of the white babies showed the infection. They concluded further that 2.8 per cent of all babies born in St. Louis were syphilitic.

It is of interest to compare these figures with the incidence of syphilis among pregnant women. Large maternity hospitals with varying races and varying economic groups present a figure varying from 5 to 8 per cent. In the studies of McCord and others syphilis occurs in about 20 per cent of pregnant negro women.

The discrepancy in the incidence of syphilis noted in the newborn as compared to what is observed in the pregnant woman is explained by two factors: first, the influence of prenatal therapy on the product of conception; and second, the natural escape of a certain percentage of infants born of syphilitic mothers.

It has been conclusively proved that adequate prenatal therapy will practically stamp out congenital syphilis. Carrying this premise to its logical conclusion, we may assume that in time congenital syphilis may become as rare as smallpox, or as we hope diphtheria will be. The tremendous problem is early diagnosis, adequate treatment, and efficient follow-up.

One has but to peruse casually the literature on the value of prenatal antisyphilitic therapy to realize that here is the complete answer to the problem of congenital syphilis.

A study made by Laurent and prepared for distribution by the American Social Hygiene Association shows strikingly the effect of antisyphilitic therapy in 213

women. The first 563 pregnancies occurred before these women received treatment, the last 161 occurred after treatment.

TABLE I

	NO. OF PREGNANCIES	MACERATED FETUSES	STILLBORN FETUSES	MISCARRIAGES	DEAD BEFORE 3 MONTHS	ALIVE AT 3 MONTHS
Untreated	563	15.0		33.74	24.68	26.46
Treated	161	0.4	5	2.5		91.87

McCord's figures among the negroes are equally illuminating. In his untreated group pregnancy ended disastrously in 66.2 per cent of the cases; in his treated group, in only 6 per cent of the cases.

In collaboration with McCord I have studied approximately 1,000 infants born of syphilitic mothers. These infants were observed for periods varying from a few weeks to eight years. Of 563 mothers receiving antisyphilitic therapy, only eighty-one, or 17.7 per cent, produced syphilitic offspring. Of 178 mothers receiving nine or more injections of neoarsphenamine (4 gm. or more) only ten, or 5.3 per cent, produced syphilitic children; that is, antisyphilitic therapy was successful in 94.7 per cent of the cases.

Compared to these figures, there were 317 syphilitic women who received no therapy; approximately 65 per cent produced definitely syphilitic offspring.

All workers have stressed the importance of early prenatal therapy—at least by the end of the fourth month of gestation, since infection of the fetus rarely occurs before this time. The importance of this point is not to be minimized, but I wish to emphasize the fact that even in the last two or three months of pregnancy treatment may be eminently successful, as was the case with a large number of our patients.

The importance of prenatal therapy in every pregnancy of a woman once proved syphilitic should be stressed. We have observed patients positive during one pregnancy, negative during another, and some years later again positive. Because of the recessive tendency of syphilis during pregnancy antisyphilitic therapy should be instituted in every instance of known infection or every instance in which there is reasonable possibility of such infection.

Accurate evaluation of prenatal antisyphilitic therapy must of necessity be long and difficult. Before any dogmatic statement can be made concerning the prophylaxis of congenital syphilis, it is probably necessary to follow a large group of children to adult life. Such a study thus far has not been made. Certain facts and figures about the appearance and behavior of congenital syphilis are known, however.

The observation has been made frequently that it is impossible to determine always with certainty the presence or absence of the infection at birth. Each of us has observed an apparently normal healthy newborn infant, whose blood Wassermann reaction was negative and yet who subsequently developed clinical and serologic evidence of the disease. In a study made on approximately one thousand infants born of syphilitic mothers, 273 showed definite evidence of the infection. Of this number, only 170, or 67 per cent, were so diagnosed at birth; the remaining 103 developed evidence of the disease subsequently. By means of monthly physical examinations and blood tests, it was found that all babies so followed showed positive evidence of the infection by the fourth month of life, with two exceptions. In these two infants, antisyphilitic treatment was instituted before the Wassermann was rechecked. It seems probable, therefore, that an infant born of

a syphilitic mother and reaching the fourth month of life without physical or serologic evidence of the disease will escape the infection.

What of the infant whose cord Wassermann reaction is positive, whose physical examination shows no syphilitic changes, and whose mother is definitely syphilitic? Rarely are these infants not syphilitic. We have observed some thirty-odd such cases and have noted the reversal of the blood test in the first few weeks of life and the failure of these babies to develop syphilitic lesions. Other observers (recently Dunham) have observed this phenomenon and believe that probably the complement-fixing substance of the mother's blood is transmitted to the infant, where it remains for a few weeks and disappears.

The so-called late manifestations of congenital syphilis seem to refute the opinion expressed above—that the infant has probably escaped infection if he reaches his fourth month without evidence of the disease. Although we are unable to answer this argument with statistics, it is our feeling that if these children showing "late syphilitic lesions" had been followed during the first four months of their lives, definite physical or serologic evidence of the disease would have been noted. Some of our children have been observed for eight years, and thus far this opinion still seems to hold good.

The problem of treatment of the offspring of the syphilitic mother is of tremendous importance. The statement made by many observers that all such infants should be treated, regardless of the physical and serologic findings, seems unjustified in the light of present knowledge. No infant should be subjected to the ordeal of adequate antisyphilitic therapy unless its indication is certain. The baby with a negative cord Wassermann reaction and negative physical examination should not be treated but should be carefully watched. The baby with a positive cord Wassermann reaction but with a negative physical examination need not be treated if careful follow-up is possible.

The positive Wassermann reaction, in the face of the negative physical findings, should be checked, and, if again positive, antisyphilitic therapy should be instituted.

Of course, the positive physical and serologic cases should be treated at once.

DISCUSSION

CHAIRMAN YAMPOLSKY.—Did the blood Wassermann reaction at birth differ from the cord Wassermann so that it justified discontinuance?

DR. ROBERTS.—The only time it is justified is when something clouds the reaction. Anticomplementary reactions occur more frequently with this blood than sinus blood. We do not regard the cord blood Wassermann reaction as final.

DR. BRIGMAN.—Clinical examinations will be a better guide in reaching a final conclusion than will the blood reaction, and the cord blood is not as reliable as blood taken from longitudinal sinus. Cord blood is unreliable for Wassermann tests.

DR. ROBERTS.—The sinus blood would be just as unreliable, but your figures checked the same anticomplementary. The point is the positive Wassermann reaction does not appear always at birth but, later, from six weeks to three months, as a rule. We have never found it appearing after the fourth month. We had only two cases that failed to bear that out.

DR. McDOWELL.—At what age do you take sinus blood for the first Wassermann reaction?

DR. ROBERTS.—At the end of the first month.

DR. BRIGMAN.—How do you explain twins, not identical, with positive blood and positive clinical syphilis in one twin and negative blood and negative physical findings in the other twin? Is it because the spirochete that is active in the mother goes through one placenta or because the placenta is possibly syphilitic in one and nonsyphilitic in the other?

I am observing two sets of twins, one child of each set being definitely syphilitic. He had every sign—positive blood reaction, physical findings, skin lesions, and so forth. The other one is a perfectly normal child and has remained so for ten years. One was syphilitic at birth and the other one was not syphilitic.

I have two other families in which the odd children are negative and the even children are positive. In the other family the reverse is true. In one family with five children, the odd ones, one, three, and five, are syphilitic; two and four are not syphilitic. The other family has four children of whom the odd ones are nonsyphilitic and the even ones are syphilitic.

DR. ROBERTS.—This phenomenon is probably due to the presence of the syphilitic infection in the blood stream. The mothers are in a recessive stage of the disease in one pregnancy and in a florid stage of the disease in the next pregnancy. That is one of the arguments advanced against germ cell transmission. If the mother who is negative during all her pregnancies—and some workers who believe very firmly in germ cell transmission report such cases—while married to a definitely syphilitic father produces a syphilitic child, and then by a nonsyphilitic father produces a perfectly normal child; of course, her case makes a strong argument for paternal transmission.

DR. PADFIELD.—In the case of the twins, is one justified in not treating the apparently normal child?

DR. BRIGMAN.—We cannot differentiate the baby who has a positive Wassermann reaction without clinical signs from the one with both positive Wassermann reaction and signs.

DR. ROBERTS.—I admit you have all the facts on your side.

CHAIRMAN YAMPOLSKY.—Have you attempted to correlate the pathologic findings in the placenta with positive or negative Wassermann reactions after birth? Have you found that the placenta showed syphilitic lesions in the patients who are negative for the first month or two?

DR. ROBERTS.—I am sorry I haven't those figures. Dr. McCord has studied that point, however.

An interesting point is the question of breast feeding in these babies. I have always had the feeling we were perfectly safe in going ahead with breast feeding regardless of diagnosis. Some authors, however, feel babies apparently normal, born of syphilitic mothers should never be breast fed, but the consensus of opinion is to go ahead with breast feeding regardless.

The Untoward Effects of the Use of Arsenicals in Children and Criteria of Cure in Treatment of Syphilis in Children

Lemuel R. Brigman, M.D.

Whatever the avenue of attack or the combination of therapeutic agents employed to combat syphilis, we must agree on two points: first, time and, second, continuity. It cannot be emphasized too forcefully that no time limit can be set

for the cure of syphilis. Opinion is united in a thorough and unremitting treatment over a period of years.[1]

The chief factor in reducing the time period is the early diagnosis and institution of a continuous form of treatment with various combinations of drugs. Late syphilis of the central nervous system is directly related to how early treatment is started. Once the nervous system is damaged, it is doubtful if a scar can be eradicated.[2] To cure congenital syphilis, it is necessary to banish every clinical symptom, to reverse every positive serologic reaction, to remove every roentgenologic evidence of the disease, and to maintain this state in the patient for a minimum period of one year without treatment.

After this time it is wise to make semiannual Wassermann tests and examinations to discover cases which do not remain cured.

A positive Wassermann reaction in the newborn child is not in itself proof that the infant has congenital syphilis because this reaction may be due to antibodies passing from the mother's blood through the placenta into the infant's blood.[3] Repeated tests will show a diminishing Wassermann reaction which in a few months becomes negative and stays negative if the infant does not have a spirochetal infection. Some authors advise withholding treatment to eliminate these cases from true syphilis, but it is important also not to deny the newborn the benefits of early treatment. Even without clinical or x-ray evidence of syphilis, the newborn with serologic evidence of the disease is entitled to a few months' treatment until all evidence of the disease has disappeared. Kolmer describes two sources of error in the Wassermann reaction: the unavoidable or biologic, and the avoidable, or technical. This transmission from mother to infant may be unavoidable or biologic, as with yaws and frambesia; but even though the biologic action may have occurred in the mother, the positive Wassermann reaction is in the infant's blood, and, since a positive reaction is evidence of spirochetal activity, the patient must be treated.

Wassermann-fast cases are often regarded as cured by syphilologists; yet we see these reactions reverse in many instances when a change of therapy is instituted.

Arsenic is an ideal treponemocide, not as toxic as bismuth, though it may cause urticaria, erythema, jaundice, pruritis, dermatitis exfoliativa, or hemorrhagic encaphalitis.[4]

The arsphenamines cause about 11.2 per cent of the reactions of various kinds, the most frequent of which is a disturbance of the gastrointestinal tract resulting in vomiting and nausea in 75 per cent of these cases; nitritoid reaction, 14 per cent, and flushing and chills in about 6 per cent.[5] Arsphenamine causes 63 per cent of the reactions; neoarsphenamine, 16.5 per cent; and sulpharsphenamine, 1 per cent. The peak of reactions come about one hour after the intravenous injections. All forms of reactions occur about one hundred times less frequently when the same drugs are given intramuscularly in children; the ideal is reached with neoarsphenamine given by the scalp method in which no systemic reaction has appeared in thirteen years of use in hundreds of patients and thousands of injections.

Ireland lists the following exanthemas: urticaria, erythema multiforme, lichen planus, herpes, keratoses, ninth-day erythema, pruritis, stomatitis, hemorrhagic cutaneous manifestation, and dermatitis. All these occurred in adults following arsenobenzols intravenously. The most frequent and severe reactions result from high dosage, rapid injections, and concentrated solutions. This prevails in infants as well as in adults.

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DISCUSSION

DR. ROBERTS.—Is there much pain at the time of the intrascalp injection?

DR. BRIGMAN.—Apparently not very much.

CHAIRMAN YAMPOLSKY.—Have you not included spinal punctures in your criteria of cures?

DR. BRIGMAN.—We do not, but I really believe it is a good thing to do.

DR. McDOWELL.—At what ages do you use the intrascalp method?

DR. BRIGMAN.—Up to the time when we can make intravenous injections without difficulty, from a few days after birth to eighteen months.

The meeting was adjourned.

ANNUAL MEETING OF REGION IV OF THE AMERICAN ACADEMY OF PEDIATRICS

THE annual meeting of Region IV of the American Academy of Pediatrics was held in Oakland, Calif., on October 26 and 27, 1934. Approximately forty-five attended. The first session was held at the Alameda County Hospital, and the two following sessions at the Children's Hospital. Luncheon was provided at the Children's Hospital, and in the evening there was an informal dinner at the Claremont Country Club. Following the morning session on the second day, a majority of the members attended the football game between Stanford University and the University of Southern California.

The program and entertainment were arranged by Dr. Clifford Sweet, of Oakland. Fourteen papers and a round table discussion of respiratory tract diseases made up the program. A few of the papers were given by invited guests. In general, papers and discussions were concisely presented and found to be of interest and value. The next annual meeting will be held in Seattle, Wash., under the direction of Dr. Jay Durand.

Abstracts of the papers follow:

The Treatment of Tetanus. Sumner Everingham, M.D., Oakland, Calif.

Study of cases of tetanus in Highland Hospital shows an incidence of slightly more than 60 per cent occurring in children. With these figures in mind, it is essential that all wounds occurring in infected areas receive not only the usual antitetanic serum but also débridement. Once the disease has become manifest, the so-called "healed" wounds should be searched for foreign body or necrotic material.

We also feel that in treatment of the disease the use of antitetanic serum has been used possibly too enthusiastically. Apparently the method of administration is more or less unimportant. An initial dose of forty to sixty thousand units should be administered, the effect lasting possibly for some five to seven days. Barbiturates and avertin should be used to avert spasms and convulsions and can be continued over long periods. Fluids, of course, are essential.

Bacillus Welchii Infection. D. D. Lum, M.D., Alameda, Calif.

There has been a marked increase in the incidence of gas gangrene during the past few years. Over 50 per cent of the cases are in compound fractures of the lower extremities. Prophylactic treatment should consist of immediate débridement plus the use of polyanaerobic serum. The dose of polyanaerobic serum should be at least doubled, as the present dosage is too small for proper prophylaxis. The usual symptoms of gangrene, subcutaneous crepitation and prostration, were enumerated. Emphasis was placed on the marked anemia due to the hemolytic action of the infection in certain cases. Treatment should consist of surgery, use of serum, and transfusion.

An Analysis of the Results in the Treatment of Pertussis With Krueger's Endoantigen. A. Lawrence Gleason, M.D., Oakland, Calif.

The paper points out that Krueger's vaccine is an undenatured vaccine prepared by grinding up mass cultures of *B. pertussis* in a special ball mill machine and filtering the fragments through an acetic collodion filter. The filtrate contains the antigen. A series of 232 treated cases with 77 per cent good results using vaccine prepared in Krueger's laboratory is compared with another series showing a large percentage of poor results. The vaccine in the second series being supplied by Lilly Laboratories. It is pointed out that the latter vaccine, until the past six months, has been very spotty and uncertain. Vaccine acts by stimulating antibodies and possibly by desensitization.

Advantages: No local reaction in arm; undenatured vaccine contains more antigen; helps as much in catarrhal stage as paroxysmal stage.

Disadvantages: Number of doses required to obtain results.

After-Treatment of Anterior Poliomyelitis. William F. Holcomb, M.D., Oakland, Calif.

The after-care of the paralytic patient was described in two general phases: the first or acute phase, lasting approximately from four to twelve weeks; the second phase, lasting from twelve weeks until the time the paralysis is considered static. In the discussion of the first phase were described satisfactory splints which could be simply made—the important principle being rest and the prevention of deformity. In the discussion of the second phase, the principal point stressed was the recovery of muscles based on their functional ability. It was pointed out that extreme care must be used and that the muscle should not be underexercised or overexercised. The optimum of contraction usually produces good results, whereas two much immobilization or overuse produces the same results, namely, atrophy. All strong-arm methods such as violent massage, excess heat, and manipulative procedures are contraindicated.

The Mechanism of Cellular Defense in Acute Pulmonary Diseases. James B. Graeser, M.D., Oakland, Calif.

Recent studies of experimentally produced pneumococcus pneumonia in dogs has afforded a more complete understanding of the mechanism of cellular defense in this disease as well as other acute pulmonary infections. The mobilization of these defenses is a methodical and rapid process. The strategy of defense in this disease, as in all infectious processes, is to localize the infection. Spread of the organisms from the original focus occurs along the alveolar walls and by growth of the organ-

isms in the serum exuded into the alveoli. Polymorphonuclear cells furnish the first line of defense. Phagocytic monocytes enter the field to complete the process. Failure of these cells to fulfill their respective duties ultimately results in unrestricted growth of the organisms, then septicemia and death.

The Follow-Up in Certain Communicable Diseases. Henry E. Stafford, M.D., Oakland, Calif.

Many communicable diseases considered to be of little consequence by the average parent may establish foci of infection, reduce the efficiency of the child through fatigue and faulty posture, and lead to psychologic maladjustments. Such sequelae can often be prevented by the physician personally contacting all children two to four weeks following communicable diseases and giving them complete physical examinations.

Nasal and Bronchial Allergy. Albert H. Rowe, M.D., Oakland, Calif.

Nasal and bronchial allergy in childhood need constant consideration by pediatricians and especially by rhinologists. The presence of eosinophiles in the nasal secretion is important evidence in favor of allergy and may arise in inhalant and in food sensitizations. Analysis of 303 cases of bronchial asthma in childhood emphasizes the importance of food allergy during the first two years of life and the increasing importance of inhalant sensitization with advancing age. Recurrent bronchitis without evidences of asthma is frequently due to allergy. Seasonal hay fever due to pollen allergy, as well as perennial hay fever due to food and inhalant sensitizations, may produce symptoms suggestive of recurrent colds or coughs, sinusitis, or pharyngitis. Many of these children have concomitant cutaneous or gastrointestinal symptoms due to allergy and may have less frequent manifestations of protein sensitization, such as low-grade fever, cyclic vomiting, and the beginning manifestations of allergic migraine. Diagnosis of inhalant allergy depends on history and scratch and intradermal testing, although the occurrence of the negative skin reaction in approximately 30 per cent of such patients must be recognized. Food sensitization is often accompanied by the negative skin reaction, and trial diets, such as the elimination diets of the writer, are of marked importance in the determination of the causative foods. The futility of surgery in the control of nasal allergy is emphasized.

Observations on Postural Treatment of Upper Respiratory Infection. Sidney N. Parkinson, M.D., Oakland, Calif.

To be printed in full in the Journal.

Pediatric Dental Teamwork. Three Cases. Charles A. Sweet, D.D.S., Oakland, Calif.

Three cases were reported showing the necessity of medicodental teamwork if dental caries is to be controlled in the child. One case showed the beneficial effects from an adequate intake of vitamin C; the second showed the necessity of the administration of vitamin D; and the third illustrated the effect of thyroid deficiency. In conclusion it was shown that there are many dietary and physical discrepancies that play most important parts in the control of dental caries. A plea was made for a more frequent formation of a medicodental team, for oftentimes the mechanical correction of dental defects is insufficient.

Résumé of "Renal Hypoplasia." Paul Michael, M.D., Oakland, Calif.

Four cases of renal hypoplasia were presented showing the various characteristics of this pathologic entity. One was the unilateral type, the other three were of the bilateral type. The various coincidental findings in this condition were also noted —namely upset in calcium-phosphorus balance resulting in demineralization and some decalcification of the osseous system. Marked infantilism of the patients with signs of hypertension and cardiac enlargement were observed. Postmortem examination revealed cardiac hypertrophy with renal hypoplasia associated with chronic interstitial nephritis. Abnormal calcium deposits were seen in the heart and kidneys. The parathyroid glands were normal throughout.

The Kidneys in 47 Consecutive Postmortems at the Children's Hospital of the East Bay. W. W. Cross, M.D., Oakland, Calif.

In a review of the kidney tissue in forty-seven postmortems performed at the East Bay Children's Hospital in Oakland, Calif., the tissue examined was normal in eleven; four could not be read because of poor fixation; six showed congestion; fifteen showed cloudy swelling; one, hypostatic congestion; and ten, nephritis. Pyelonephritis was not found although it is frequently observed clinically in children. In those patients who had nephritis, death was due to infection, largely respiratory. Two infections only were clinically nephritis. The tissue when read suggested that those patients recovering from their illness will have a foundation laid for trouble later in life. Portions of the kidney are found damaged, past recovery, and probably many lesions found in the adults have their foundation in an illness of early childhood. Congenital defects of the urinary tract were not observed in the series.

Wilms Tumor. Edward S. Babcock, M.D., Sacramento, Calif.

A previously healthy two-and-one-half-year-old girl vomited and passed bloody urine on May 16, 1934. Physical examination revealed a large, hard mass filling the right side of the abdomen. Pyelogram of right kidney showed marked rotation and displacement. On May 19, 1934, a 450-gm. embryoma, or Wilms tumor, predominately of sarcomatous nature was removed. Postoperative x-ray therapy was given. Symptoms of metastases appeared seven weeks later, starting with low backache, complete paralysis of lower extremities and sphincters, and anesthesia below the pectoral region. Patient expired Aug. 27, 1934. Autopsy showed many visceral metastatic nodules as well as compression of the cord at the level of the first and second thoracic vertebrae by an extradural growth involving the bodies of these vertebrae. Microscopic sections of the metastases showed a structure similar to that of the parent tumor. Microphotographs were shown and a brief account of these tumors was given.

Streptococcus Viridans Septicemia With Recovery. Enos Paul Cook, M.D., San Jose, Calif.

A previously healthy girl, aged five years, was recovering from an acute upper respiratory infection with suppurative otitis media, when she suddenly developed chills and fever up to 105° F. Mastoiditis was diagnosed roentgenologically and mastoidectomy performed; the sigmoid sinus was exposed and no thrombosis found; a blood culture showed a pure growth of *Streptococcus viridans*. A transfusion of 250 c.c. of whole blood was given intravenously from the mother. No improvement followed; the chills and fever continued, and joint pains made their appearance. Six days later another blood transfusion of 275 c.c. was given, the donor this time being

a maternal uncle who was four weeks convalescent from a throat infection. Throat culture of this donor taken at the time of his illness showed *Streptococcus viridans*. His selection was because of his possible value as a specific immune donor. The patient's condition remained about the same for another week, when another transfusion, of 200 c.c., was given. Six days later there was a dramatic drop in temperature followed by complete and permanent recovery. Total duration of febrile period from the initial chill was twenty-three days. Symptomatic and supportive measures supplemented the treatment by transfusions. Tonsillectomy was performed seven months after illness, and the culture taken from the tonsil immediately upon removal showed *Streptococcus viridans*.

Laryngotracheobronchitis. Report of Three Cases. Clifford Sweet, M.D., Oakland, Calif.

Since 1920 nondiphtheritic laryngitis has been recognized as a serious and frequently fatal disease of childhood. It may be preceded by an upper respiratory tract infection or may appear without prodromal symptoms. Laryngeal obstruction may be constant or may be so periodic in character that the seriousness of the condition is not recognized until too late for treatment. The first patient was admitted moribund and recovered after tracheotomy. The second recovered from the obstructive laryngitis with expectant treatment but developed bronchopneumonia, purulent pericarditis, influenzal and staphylococcus septicemia and a terminal bilateral empyema. The purulent pericarditis was treated by a method, which so far as the author knows, was original, i.e., a trocar was passed into the pericardium by way of the left sternozyphoid angle and an indwelling catheter was placed for pericardial drainage. This means of draining the pericardium was so evidently adequate that it would seem well to use it in future cases. The third child did well for a time after tracheotomy but died from a complicating influenzal meningitis. All three cases reported yielded pure cultures of *Staphylococcus albus* and influenza bacillus, suggesting a symbiotic action of these organisms. All cases of laryngobronchitis should be regarded as dangerous, and the patients should be placed in the hospital with facilities for tracheotomy immediately available.

PEDIATRIC SERVICE IN GENERAL HOSPITALS

Report of the Committee on Hospitals and Dispensaries of the American Academy of Pediatrics

IN THE following series of reports we shall attempt to present at least a partial picture of pediatric care and facilities for that care in the pediatric departments of general hospitals throughout the United States. Questionnaires were sent only to hospitals having at least twenty-four beds exclusively for children. Bassinets were counted in the pediatric service when the service was under the direction of a pediatrician.

The first report concerns the hospitals in Region I of the Academy of Pediatrics. This region includes the following states: Connecticut, Delaware, Maine, Maryland, Massachusetts, New Jersey, New York, Pennsylvania, Rhode Island, and the District of Columbia. This particular area is, of course, the most thickly populated in the entire country.

Total Beds.—The total number of beds and bassinets by states is given in Table I:

Table I

STATE	NUMBER HOSPITALS	BEDS	BASSINETS	HOSPITAL WITH LARGEST NO. BEDS	HOSPITAL WITH SMALLEST NO. BEDS	HOSPITAL WITH LARGEST NO. BASS.	HOSPITAL WITH SMALLEST NO. BASS.
Conn.	10	437	422	86	27	100	7
Del.	1	35	5	0	0	0	0
Maine	4*	56	42	32	24	28	14
Maryland	2	92	56	59	33	35	21
Mass.	16†	719	665	188	26	218	8
N. J.	11	474	395	90	26	98	3
Pa.	36	1,492	2,522	193	24	65	0
R. I.	3	237	94	147	42	43	21
N. Y.	50‡	3,133	1,403	326	25	127	0
D. C.	2	160	145	100	60	100	45

*Two reported.
†Fifteen reported.
‡One did not report.

In the entire region there are 135 hospitals which have a pediatric service of twenty-four or more beds and bassinets. Four of these did not reply to this part of the questionnaire.

Among all the hospitals we find a total of 6,835 beds for children and 5,749 bassinets. The largest service has 326 beds for children; the smallest, twenty-four. The largest number of bassinets in any one hospital is 218; the smallest, seven. New York State has fifty* hospitals maintaining at least twenty-four beds exclusively for children. Pennsylvania has thirty-six. No other state has more than sixteen, and Delaware reports only one.

Residents.—Among the 131 hospitals considered in this report, thirty-three employ resident pediatricians. Over half of this number are employed in New York State alone. Twenty-nine residents are employed exclusively in the pediatric department, and in most instances they are paid a salary which varies from $25 to $175 per month.

*One hospital did not reply to this part of the questionnaire.

Internes.—The question on interneships was designed to reveal the number of instances in which internes served exclusively in the children's department or merely went there for part of a rotating general interneship. Several replies were indefinite in this distinction. In as far as we could determine, thirty hospitals employ internes on a service confined exclusively to pediatrics. Fifteen such services are in New York. Ninety-four hospitals report that the internes come to the pediatric department as part of the service of a general interneship. Three hospitals apparently employ neither residents nor internes. The length of time spent on the service varies from one to six months. In most instances the service is for three months.

Attending Staff.—The total number of attending pediatricians for the 131 hospitals is 540. The length of time for these respective services varies from one to twelve months. The majority of the services are for six to twelve months. There are a few services as short as one, two, or three months.

Newborn Service.—Sixty-seven hospitals maintain newborn services under the care of the pediatric department. No hospital in Delaware, Maine or Maryland reports that they have such a service. New York has 26; Pennsylvania 17; no other state has more than 9.

Nursing.—One hundred sixty-one registered nurses are employed as heads of the pediatric departments, among these hospitals. Very few employ more than one head nurse, and there are a few which have none for that department alone. One hundred and twenty-one of these head nurses have had special pediatric training. In many instances, however, the special training has consisted of only a three-month course or even less. Pupil nurses serve in the pediatric department in practically all of the hospitals. The usual length of the service is from three to four months.

As near as can be determined, the average ratio of nurses to children and infants is 1:4. In a few instances it ran as high as 1:9 or 12.

Social Service.—Fifty-six hospitals maintain a special social service for children. Among these forty-two are in New York and Pennsylvania.

Diet Kitchen.—One hundred twenty-five hospitals maintain special diet kitchens for infants, sixty-five for children.

Schooling and Recreation.—Schooling for convalescents is provided in forty-six hospitals, and ninety-three provide recreation facilities.

Dispensary.—One hundred thirteen hospitals maintain a special department for children in the dispensary. In many instances this department is open only two or three times weekly. Average attendance in a few of these dispensaries is as low as four or five patients each session, while many have forty or more. Average attendance is somewhere between twenty and thirty children. Replies to the question concerning clinic attendance did not permit us to compile very accurate figures. The pediatric staff serves in both hospital and dispensary in 104 hospitals. The resident sees service there in twenty-four instances; the interne in eighty-five.

Table II shows the number of children and newborn cared for by these hospitals in 1933, together with number of deaths, autopsies and percentage of autopsies, and deaths among the newborn and children.

DISCUSSION

In reading the above report, one must bear in mind that 12,584 does not represent the total number of beds and bassinets available for children in the hospitals of Region I. There are many other hospitals in which children are admitted regularly as patients but in which the number of beds and bassinets is less than twenty-four. In the latter hospitals there is probably no regular pediatric service.

There are several interesting facts presented by Table I. Among these, five, or one-half of the states in the region considered, have only ten hospitals with services for children large enough for consideration under the standard of this report.

The smallest number of beds for children in any one service reported is twenty-four, the largest 326; similarly for bassinets, none and 218. The largest children's

TABLE II

	NEWBORN	CHILDREN	NEWBORN DEATHS	CHILDREN'S DEATHS	NEWBORN AUTOPSIES	CHILDREN'S AUTOPSIES	PERCENTAGE NEWBORN AUTOPSIES	PERCENTAGE CHILDREN'S AUTOPSIES	PERCENTAGE NEWBORN DEATHS	PERCENTAGE CHILDREN'S DEATHS
Conn.	6,597	7,338	213	211	51	72	23.9	34.1	3.2	2.8
Del.	429	1,303	18	26	3	11	16.6	42.3	4.1	1.9
Maine	462	648	16	12	3	8	18.7	66.6	3.4	1.8
Maryland	836	1,314	7	66	5	23	71.4	34.8	0.84	5.2
Mass.	10,874	15,386	377	440	72	117	19.0	26.5	3.4	2.8
N. J.	18,829	15,508	369	540	96	130	26.0	24.0	1.96	3.4
N. Y.	38,053	47,346	1,144	2,588	604	1,174	52.7	45.3	3.0	5.4
Pa.	20,456	24,490	695	906	246	323	35.3	35.6	3.3	2.8
R. I.	906	1,167	44	89	16	52	36.3	58.4	4.8	7.6
D. C.	2,663	2,223	114	204	89	86	78.0	42.1	4.2	9.1
Total	100,105	116,723	2,997	5,082	1,185	1,996	39.5	39.2	2.9	4.3

service is in New York, the smallest in Maine and Pennsylvania. The largest infant (bassinets) service is in Massachusetts (218); the smallest, in New Jersey (3). One hospital in both Pennsylvania and New York reports that it has no bassinets which may mean either there are no newborn there or that the pediatric department has nothing to do with that service. New York alone has more twenty-four-bed services than all other states combined, excluding Pennsylvania; New York, 49; all other states combined excluding Pennsylvania, 46. Pennsylvania has 36, only thirteen less than New York; New York and Pennsylvania combined, over half, or 57 per cent, of all such hospitals in Region I. Sixty-seven plus per cent of all beds are in these two states, 68+ per cent of all bassinets. These figures are accounted for by the relatively large population of these two states.

Comparatively few of the hospitals employ a pediatric resident. This is to be expected as there are few large pediatric departments among these hospitals. We have no information concerning the requirements of qualification for these positions.

In thirty hospitals internes may be employed for one year on the pediatric service. In most instances the service is for three months as a part of a general rotating internship. A few report one-month internships. This seems too short a time for practical value either to the hospital or to the interne.

Only 67 hospitals, or 51 per cent, include the newborn service as part of the pediatric department. We feel that the newborn service should always be under the supervision of the pediatric department.

Only a few hospitals lack a head nurse whose duties are limited to the pediatric department. In most instances only one head nurse is employed. Among the 161 nurses reported employed in this capacity, 40 have not had special pediatric training, and in many other instances special training has consisted of only three-month, or shorter, courses. We fail to see how these individuals can properly qualify for duties as a head nurse in the care of infants and children.

In practically all of the hospitals there seems to be enough nurses for adequate care as far as number is concerned; as to the efficiency of their training we have no information.

Only the larger hospitals have social service departments which confine their duties to children alone. Of the fifty-six departments reported, forty-two are in New York and Pennsylvania.

A surprisingly large number of hospitals (125) report special diet kitchens for infants. This large number is probably accounted for by the fact that formula or milk "labs" are counted as diet kitchens.

Eighty-five hospitals report no facilities for schooling, and thirty-eight, no facilities for recreation. Part of the shortcoming in these important activities is probably accounted for by the fact that the services are relatively quite small, and very few children are confined to the hospital for long periods of time.

News and Notes

The following men have been certified by the American Board of Pediatrics since the last report:

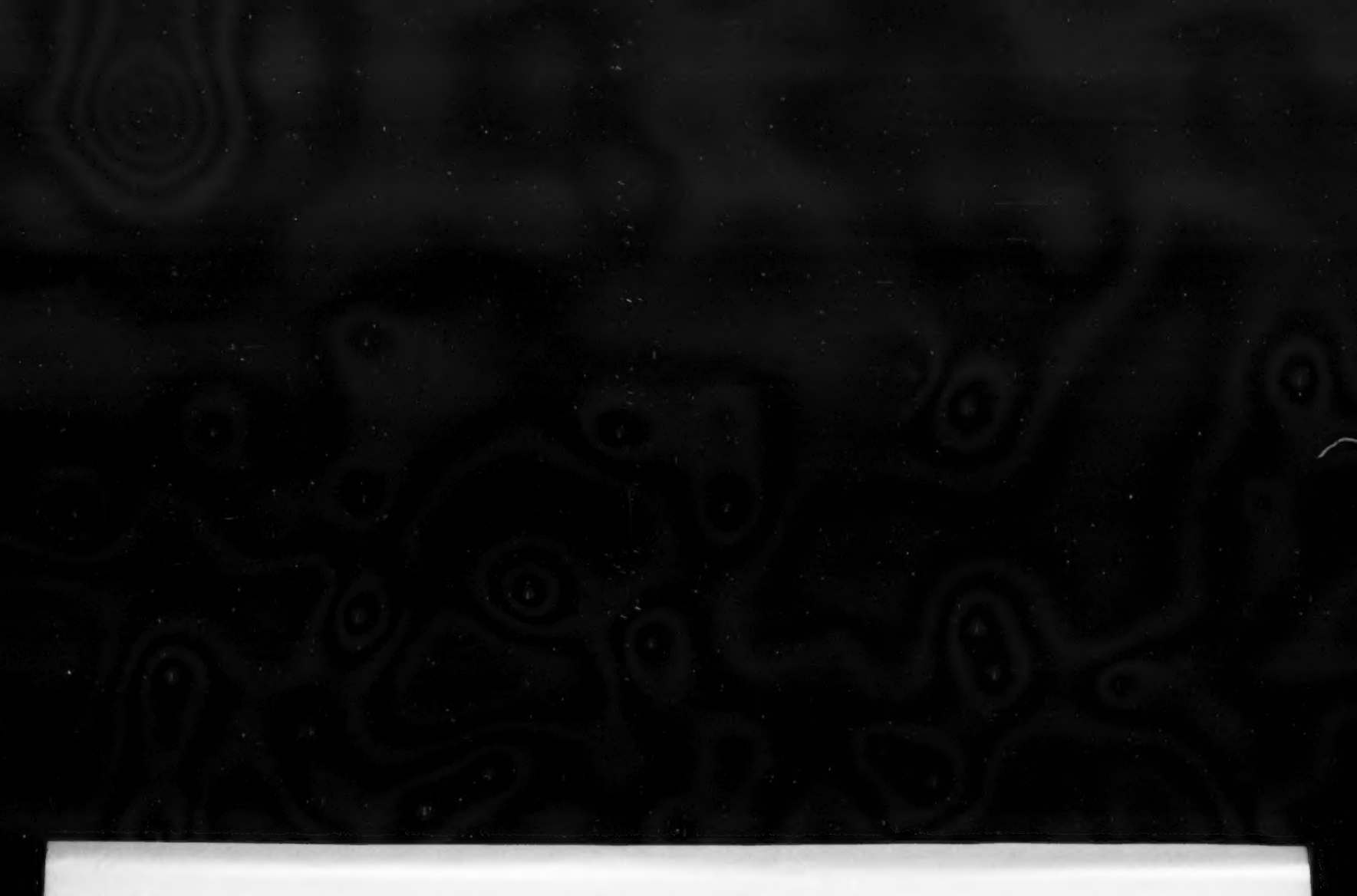
Sterling Hindley Ashmun, Dayton, Ohio
Walter C. Bacon, Baltimore, Md.
Henry Lambert Bibby, Kingston, N. Y.
Thomas Ellwood Buckman, Jacksonville, Fla.
Craig D. Butler, Oak Park, Ill.
Harvey F. Garrison, Jackson, Miss.
John King Glen, Houston, Texas
Hyman Green, Boston, Mass.
Paul M. Hamilton, Alhambra, Calif.
Oliver W. Hill, Knoxville, Tenn.
Hughes Kennedy, Jr., Birmingham, Ala.
Jacob Carl Krafft, Chicago, Ill.
James G. Kramer, Akron, Ohio
Frank H. Lancaster, Houston, Texas
Abraham Levinson, Chicago, Ill.
Edgar W. Loomis, Dallas, Texas
T. C. McCrummen, Austin, Texas
Henry S. Meyer, Houston, Texas
Frederick Bingham Miner, Flint, Mich.
J. Buren Sidbury, Wilmington, N. C.
Lewis K. Sweet, San Antonio, Texas
William M. Taylor, Oklahoma City, Okla.
T. A. Tumbleson, Beaumont, Texas
Damon Walthall, Kansas City, Mo.
Antonio J. Waring, Savannah, Ga.
C. H. Webb, Shreveport, La.
Carl Edward Weigele, Jersey City, N. J.
Noel C. Womack, Jackson, Miss.
Edward J. Wynkoop, Syracuse, N. Y.

Comments

THE wisdom of "seeing ourselves as others see us" is beyond question. The recently translated book, *American Medicine*, by Dr. Henry Sigerist, is not only delightful reading, but it is also a clear-cut picture of the development, changes, and present tendencies of medicine in the United States written by an historian who was eminently qualified for the task and who has succeeded with his subject in an admirable way. What makes it of particular value is that it was written in German for sale in Europe and that the English edition was not planned at the time the book was written. This, together with the scholarly way the material has been handled, makes it a most important document in "seeing ourselves as others see us." The author views us with an unbiased unemotional perspective that is difficult for those who are living "in the picture." There are two chapters of particular importance in our present-day confusion—"The Physician and Patient" and "Preventive Medicine." Dr. Sigerist sees nothing else possible but some form of insurance for the entire population. "American Medicine is at a crossroads. . . . American Medicine is faced with the greatest task of all . . . now that the scientific problem is solved, it must find the social solution. . . . A new frontier has been opened and calls for another generation of pioneers." Whether or not we agree with the opinions and conclusions, these detached unbiased views must be respected. It is tempting to quote again and again from the text, but we will limit ourselves to the following bit of wisdom:

"'Research' is a word to conjure with, rolled on the tongue of the youngest student. Sometimes he may think he is carrying on research when he is merely counting the buttons on his own coat and comparing them with his neighbor's; in the first enthusiasm he does not always differentiate between the essential and the non-essential. There are scientific tasks, countless as the sands of the sea, which are in themselves scientific and yet have no scientific significance. A great deal of energy is wasted in this way."

To every physician who has the slightest interest in the past, present or future of American medicine, we recommend the reading of this book. Dr. Sigerist, who has recently left the University of Leipzig, where he was professor of the history of medicine and in charge of the Institute of the History of Medicine, to become the Welch professor of the history of medicine at Johns Hopkins, has already rendered an important service to his newly adopted country.



The Journal of Pediatrics

CONTENTS FOR FEBRUARY, 1935

Original Communications

The Intravenous Administration of Fat. L. Emmett Holt, Jr., M.D., Herbert C. Tidwell, Ph.D., and T. F. McNair Scott, M.D., Baltimore, Md. 151

Prenatal Influence in Rickets. I. Fetal Rickets. John Mott Rector, M.D., San Francisco, Calif. 161

Prenatal Influence in Rickets. II. Early Postnatal Rickets and Florid Rickets With Multiple Fractures. John Mott Rector, M.D., San Francisco, Calif. 167

A Rare and Peculiar Form of Acute Interstitial Pneumonia. Myer Solis-Cohen, M.D., Philadelphia, Pa. 178

Tracheobronchial Obstruction Produced by Tuberculous Lymphadenitis. Joseph B. Bilderback, M.D., and Carl G. Ashley, M.D., Portland, Ore. 199

The Tuberculin Patch Test. J. I. Waring, M.D., Charleston, S. C. 202

Exophthalmic Goiter Before One Year of Age. Philip C. Elliott, M.D., Nashville, Tenn. 204

Clinical Record and Postmortem Pathology of Diabetic Children. Henry J. John, M.D., Cleveland, Ohio 211

Perimeningitis. Edgar E. Martmer, M.D., and Grover C. Penberthy, M.D., Detroit, Mich. 226

Pulmonary Lesions Resembling Pneumonia as the Result of Allergic Shock. George L. Waldbott, M.D., and A. D. Snell, M.D., Detroit, Mich. 229

Roentgenologic Studies of the Infant's Gastrointestinal Tract. John S. Bouslog, M.D., T. D. Cunningham, M.D., James P. Hanner, M.D., James B. Walton, M.D., and Harold D. Waltz, M.D., Denver, Colo. 234

Critical Review

Normal Nutrition During Childhood. Julian D. Boyd, M.D., Iowa City, Iowa 249

American Academy of Pediatrics

Proceedings: Fourth Annual Meeting of the American Academy of Pediatrics. Round Table Conference on Syphilis 262

Proceedings: Annual Meeting of Region IV of the American Academy of Pediatrics 277

Proceedings: Pediatric Service in General Hospitals 282

News and Notes

News and Notes 285

Comments

Comments 286

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